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EVALUATION CHARACTERISTICS OF DIABETIC KETOACIDOSIS IN CHILDREN IN SAUDI ARABIA

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Abstract

Objectives: *To evaluate the clinical and biochemical characteristics of children with diabetic ketoacidosis (DKA).*
Methods: *In this retrospective study conducted from January to October 2018 in Saudi Arabia we evaluated pediatric DKA admissions from 2014-2018. From the case files, we obtained information related to patients' age, gender, weight, presenting complaints, serum biochemical profile, and management.*
Results: *This study included 373 DKA admissions with a median age of 11 years (interquartile range [IQR]: 8-13). The patients in the subgroup of age more than 10 years old had the highest proportion of admissions (n=250, 67%, p <0.000). The median duration of diagnosis of diabetes mellitus (DM) was 3 years (IQR: 2-6). New-onset DM was 47%. Predominant precipitating cause was acute illness, mostly viral syndrome in 22% of all cases, and non-compliance to insulin regimen was in 79% of the diagnosed diabetic cases. Blood glucose, pH, anion gap, serum osmolality, serum potassium, and serum phosphate showed the highest change during the initial 6 hours of management, while trends of serum bicarbonate and blood urea nitrogen demonstrated a predominant change in the initial 12 hours.*
Conclusion: *The notable findings in this study, such as, higher mean age of presentation, high rate of non-compliance to insulin as the cause of precipitation, and a high prevalence of abdominal pain at presentation should be followed up with further comparative studies.*
Keywords: *DKA, Children, Saudi Arabia.*

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INTRODUCTION:

Diabetes mellitus (DM) is an endocrine disease affecting millions of children worldwide [1-3]. Diabetic ketoacidosis (DKA) is one of the serious complications of diabetes in the pediatric population [4], and its prevalence increases by an annual rate of 3% worldwide [3]. It is associated with significant risk of life threatening complications [5-8]. The criteria for diagnosis of DKA in children by the International Society for Pediatric and Adolescent Diabetes describes DKA as blood glucose >11 mmol/L, venous pH <7.3, or bicarbonate <15 mmol/L, and ketonemia with ketonuria [9]. Previous studies [1,2] have reported characteristics of DKA patients based on different geographical areas. Overall, there is a paucity of literature on this particular aspect. The aim of this study was to assess pediatric patients presenting with DKA regarding aspects of demographics, presentation, investigations, and management in the Kingdom of Saudi Arabia (KSA).

METHODS:

This study was conducted from January to October 2018 in Saudi Arabia. The DKA admission between 2014-2018 was identified. Inclusion criteria were patients admitted due to DKA, and were less than 14 years old. We identified the DKA admissions (n=394) from the computerized data system. To be accurate in enrollment, we verified that an admission criterion was consistent with DKA definition by the International Society for Pediatric and Adolescent Diabetes [6,7]. We then verified the completeness of the charts. Exclusion criteria were patients with incomplete documentation of DKA episode despite the system labeling them as DKA. Twenty-one patients were excluded, and the remaining 373 were the study subjects, and we searched the medical record, and extracted data related to the information regarding demographics, clinical presentation, investigations, and management. All the reported results had proper documentation. Those findings that had unclear documentations were neither included in the data, nor in the analysis, and were reported as missing. The major variables included age, gender, location of admission, co-morbidities, various presenting symptoms, non-compliance to health team instructions, duration of stay in the pediatric emergency room, Glasgow coma score (GCS), weight, acid base status, serum chemistry, hemoglobin A1c (HbA1c), immune panel, insulin therapy, and fluid/electrolyte management. Literature was searched through PubMed. We used mesh headings of DM, DKA, pediatrics, admissions, history, presentation, diagnosis, biochemical profile, investigations, and management. Non-compliance

was assessed based on the history of non-adherence to prescribed insulin regimen. Self-administered insulin was assessed based on the mode of dosing if being taken by the patients themselves.

We recorded the data on Microsoft Excel version 2007. The data were then exported to IBM Statistical Package for Social Sciences statistics version 20 (IBM Inc., Armonk, New York, USA) for further analysis. The continuous variables were evaluated for the distributions via Kolmogorov-Smirnov test, and are reported as means or medians. Further, we evaluated means via one-sample non-parametric tests using one-sample chi-square test, or one-sample binomial test. The significant level for results was set at p<0.05.

RESULTS:

We identified 373 admissions as per inclusion criteria from 2014-2018. A total of 269 patients had 373 admissions. Sixty-seven patients had more than one admission-related-DKA. In Table 1, we present the demographics of the study subjects. Only subjects with complete documentation are included and reported. The study subjects had a median age of 11 years (interquartile range [IQR]: 8-13). When dividing age into sub-categories of less than 5 years (n=41, 11%), 5-10 years (n=82, 22%), and 11-14 years (250/67%), we found a clinically significant difference among these categories (p<0.005). Regarding the gender ratio, there were slightly more female patients than males (n=207, 55.5% versus n=166, 44.5%). We found that the median duration of diagnosis of DM was 3 years (IQR: 2-6). At presentation, almost half of the DKA patients (n=157/334, 47%) were new-onset DM. Moreover, approximately one out of 5 (n=78/354, 22%) presented with an acute illness mostly viral upper respiratory tract infections, or viral gastroenteritis as the precipitating factor. On the contrary, non-compliance to insulin regimen was found in approximately 4 out of 5 (n=81/102, 79.4%). With regard to presenting complaints, we found that most patients had a history of vomiting of at least one-day duration (n=229/309, 74%) and approximately two-thirds of the patients had abdominal pain (n=203/294, 69%). Patients who had co-morbidity with another chronic disease was 16%, and only one patient was found to have co-existing psychiatric disease. More patients were admitted at the Pediatric Intensive Care Unit (PICU) than the wards (197/53% versus 176/47%). Regarding fluid management in the emergency room, almost half of the patients did not receive any fluid bolus (181/48% versus 188/52%) while subjects receiving 10 ml/kg of normal saline were the second in frequency (112/373, 30%). In our

study, the median duration of insulin infusion was 20 hours (IQR: 12-28).

In Table 2 we present clinical outcomes in DKA study subjects presenting with new-onset DM versus diagnosed DM. The study subjects had mean ages of 9 years and 11 years belonging to new-onset DM and diagnosed DM. There was a significant difference in age sub-groups. Similarly both groups showed significant difference regarding the presence of other acute and chronic conditions. The average duration of polyuria was 13 days in patients with new-onset DM as compared with 2 days in diagnosed DM, while the number of patients admitted at the PICU was almost the same. Table 3 shows the 12-hour trend related to acid base status and serum chemistry results along with other significant laboratory results. The tests were conducted in the hospital laboratory, which is of international standards and accredited by Joint Commission of accreditation. In this study, we found consistent improvement in acid base status and serum chemistry. Blood glucose, pH, anion gap, serum osmolality, serum potassium and serum phosphate showed the highest change during the first 6 hours. On the contrary, trends of serum bicarbonate and blood urea nitrogen were more linearly related to the time scale of 12 hours. Regarding white blood cell count, there was a bimodal response. In Table 4, we present immunologic profile including the islet cell antibodies (ICA), insulin antibodies (IA), and anti glutamic acid decarboxylase antibodies. Basic microbiology profile shows a low yield in tests including urinary nitrites, urinary white blood cells, blood cultures and urine cultures.

Table 1 - Clinical outcomes of subjects in a study on pediatric diabetic ketoacidosis Saudi Arabia (N=373).

Variables	Valid documentation (n)	n/median	(%) or IQR	*P*-value
Patients' demographics				
Age, years	373	11	8-13	NA*
Age categories	373			
Less than 5 years		41	(11.0)	0.000†
5 to 10 years		82	(22.0)	
More than 10 years		250	(67.0)	
Gender, male		166	(44.0)	0.038
Weight (kg)	373	31	17-39	
Characteristic features in history				
New-onset diabetes	334	157	(47.0)	0.379
Existing diabetes mellitus (DM)	334	177	(53.0)	
Duration since diagnosed as DM, years	177	3	2-6	NA*
Non-compliant to insulin therapy, yes	102	81	(79.4)	0.000
Insulin self-administered	112	47	(42.0)	0.000
Co-existing chronic medical disease	237	38	(16.0)	0.000
Co-existing psychiatric disease	4	1	(0.25)	0.000
Acute illness precipitating DKA, yes	354	78	(22.0)	0.000
Type 1 DM, yes	373	359	(96.0)	0.000
History of vomiting, yes	309	229	(74.0)	0.000
History of abdominal pain, yes	294	203	(69.0)	0.000
Duration of polyuria at presentation, days	351	3.00	0-14	NA
Characteristic features in management				
Duration of stay in the ER after being seen by the physician, hours	373	6	3.6-9.7	NA
Location of admission, PICU	373	197	(53.0)	0.222
Glasgow Coma Scale, Admission	373	15	15	NA
Deep venous thrombosis	373	0	-	NA
Brain edema, CT scan	72	0	-	NA
Duration of insulin infusion, hours	373	20	12-28	NA
Fluid bolus-normal saline	373			0.000
No fluid bolus		181	(48.5)	
Fluid bolus 10 ml/kg		112	(30.0)	
Fluid bolus 20 ml/kg		76	(20.3)	
Fluid bolus >20 ml/kg		4	(1.0)	

*p values for numerical variables are not computed, †p values for categorical variables are computed using non-parametric one-sample chi-square, or one-sample binomial tests. IQR - interquartile range, NA - not applicable, DKA - diabetic ketoacidosis, ER - emergency room, PICU - Pediatric Intensive Care Unit, NA - not aplicable

Table 2 - Clinical outcomes of study subjects in terms of new-onset versus diagnosed diabetes mellitus (DM) in a study on pediatric diabetic ketoacidosis (DKA), Saudi Arabia (N=373).

Variables	DKA in new-onset DM	DKA in diagnosed DM	
	N (%) or mean (CI)	N (%) or mean (CI)	*P*-value
Age, years	9 (8.5-9.7)	11 (10.5-11.5)	NA*
Age categories			0.002†
Less than 5 years	35 (85.0)	6 (15.0)	
5-10 years	63 (77.0)	19 (23.0)	
More than 10 years	59 (24.0)	191 (76.0)	
Gender, male	78 (47.0)	88 (53.0)	0.311
Weight, kg	29.7 (26.9-32.5)	31 (28.8-33.3)	NA
Hgb A1C (%)	12 (11.2-12.8)	12.2 (11.6-12.9)	NA
Co-existing chronic medical disease	10 (26.0)	28 (74.0)	0.009
Co-existing psychiatric disease	1 (100)	0	NA*
Acute illness precipitating DKA, yes	31 (40.0)	47 (60.0)	0.031
History of vomiting, yes	84 (37.0)	145 (63.0)	0.000
History of abdominal pain, yes	97 (48.0)	106 (52.0)	0.378
Duration of polyuria at presentation, days	13 (11.4-15.2)	2 (1.3-2.9)	NA
Duration of insulin infusion, hrs	23.8 (15.9-13.7)	21 (18.5-25)	NA
Location of admission, PICU	97 (49.0)	100 (51.0)	0.333
Normal saline fluid bolus			0.000
No fluid bolus	122 (67.0)	59 (33.0)	
Fluid bolus 10 ml/kg	56 (50.0)	56 (50.0)	
Fluid bolus 20 ml/kg	49 (64.0)	27 (36.0)	
Fluid bolus >20 ml/kg	4 (75.0)	1 (25.0)	

*p for numerical variables are not computed. †p for categorical variables are computed using non-parametric one-sample chi-square, or one sample binomial tests. CI - confidence interval, PICU - Pediatric Intensive Care Unit

Table 3 - Laboratory outcomes of the subjects in a study on pediatric diabetic ketoacidosis in Saudi Arabia.

Variables	Admission	At 6 hours	At 12 hours
pH	7.15 ± 0.11	7.28 ± 0.09 $p=0.08*$	7.32 ± 0.05 $p=0.568$
Glucose, mmol/L	27.8 ± 12.9	13.9 ± 5.9 $p=0.05$	12.8 ± 6.2 $p=0.013$
Bicarbonate, mmol/L	11.6 ± 5.1	13.7 ± 4.9 $p=0.79$	15.5 ± 11.1 $p=0.000$
Sodium, mmol/L	133 ± 4.8	135.61 ± 3.5 $p=0.143$	135 ± 4.3 $p=0.034$
Osmolality, mOsm/kg	309 ± 14.8	280 ± 7.5 $p=0.766$	282 ± 14.4 $p=0.42$
Anion gap	23 ± 5.9	12 ± 6 $p=0.006$	11 ± 6.5 $p=0.002$
Blood urea nitrogen, mmol/L	5.1 ± 1.9	3.8 ± 1.6 $p=0.006$	3.2 ± 1.5 $p=0.000$
Potassium, mmol/L	4.47 ± 0.63	4.03 ± 0.66 $p=0.262$	3.84 ± 0.59 $p=0.056$
Calcium, mmol/L	2.34 ± 0.37	2.17 ± 0.26 $p=0.313$	2.05 ± 0.28 $p=0.260$
Magnesium, mmol/L	0.83 ± 0.15	0.79 ± 0.17 $p=0.128$	0.73 ± 0.15 $p=0.493$
Phosphate, mmol/L	2.79 ± 0.14	0.96 ± 0.36 $p=0.336$	0.82 ± 0.37 $p=0.479$
White blood cells $(x10^3/mm^3)$	13 ± 7	18 ± 8 $p=0.158$	11 ± 5 $p=0.409$
Platelets, $x10^3/mm^3$	381 ± 111	387 ± 82 $p=0.593$	321 ± 89 $p=0.34$

*One-sample Kolmogorov-Smirnov test used to assess distribution. p<0.05 is significant. Values are expressed as mean + standard deviation

Table 4 - Immunological, microbiological and endocrine outcomes in a study on pediatric diabetic ketoacidosis in Saudi Arabia (N=373).

Variables	n (%)	*P*-value
Islet antibodies, positive	27 (59.0)	0.000
Insulin antibody, positive	24 (80.0)	0.002
AGAD antibody, positive	14 (61.0)	0.004
Urinary nitrites, positive	26 (6.9)	0.000
Urinary WBC, positive	29 (7.8)	0.000
Blood culture, positive	1 (0.4)	0.000
Urine culture, positive	3 (1.1)	0.000

AGAD - anti glutamic acid, WBC - white blood count

DISCUSSION:

We found 373 admissions in 5 years of study period. Predominant age group in our study regarding the number of admission was group age 10-14 (250/373, p 0.000). Forty seven percent of our study subjects had new-onset DM consistent with previously reported prevalence from 15 to 67 [5,10]. Again, we found that the number of new-onset cases were highest in patients 10-14 years (89/157, p=0.001)

while this had been reported to be highest in younger age groups [11]. It may be associated with the fact that in our study, the proportion of admissions of age group of 10-14 years is also the highest.

This study found that non-compliance to insulin regimen in diagnosed diabetics was high (79%). In a recent study, *Randall et al* [12] reported that insulin discontinuation was the leading precipitating cause in

68% of patients; other causes were new-onset diabetes (10%), infection (15%), medical illness (4%), and undetermined causes (3%). The exact reason for non-compliance is not known. Some plausible reasons may be related to non-adherence to health team instructions, and lack of proper follow up. Further, we checked whether non-compliance rate was different in various age groups, and found that there was only a minor difference that was clinically insignificant (p=0.194). Implying these findings with the fact that DKA, being a preventable disease, we suggest that strategies, such as family counselling, patients' education, and improved follow up may help to overcome non-compliance to insulin therapy, and to improve patient care, and reduce the cost of health care.

Regarding presenting complaints, we found a substantial number of patients presenting with abdominal pain (69%). Umpierrez and Freire [13] while evaluating 189 adult patients with DKA reported abdominal pain to be present in 46% of cases. Our study is different in terms of patient population with emphasis on pediatric population. Clinicians keeping this fact in consideration can avoid unnecessary investigations. We suggest a more larger scale studies particular in this aspect.

The degree of severity of DKA at presentation in our study (mean PH: 7.15+0.11) was lower as compared with other reported studies [14]. The possible reason may be due to an early access to hospital care for the study population. Cerebral edema had been reported to occur in 0.3-1% of children with DKA, and has a mortality rate of 21-24% [15,16], while in our study there is no episode of cerebral edema. This may be attributed to the milder presentation along with strict adherence to International Society for Pediatric and Adolescent Diabetes (ISPAD) DKA management protocol. Likewise, there is no mortality in our study. Many studies have reported prevalence of ICA, IA, and anti glutamic acid decarboxylase antibodies (GAD-Ab) [17-19]. We found ICA positive in 59%, IA positive in 80%, and anti GAD-Ab positive in 46% of admissions (Table 4). We report these results to provide the data related to our patient population, and to look for future studies for wider comparison. With regard to identification of infection in DKA, our study found results consistent with previous studies, and showed a low positive yield regarding urinary nitrite (6.9%, p=0.000), blood cultures (0.4%, p=0.000), and urine cultures (1.1%, p=0.000)(Table 4) [20,21]. Flood and Chiang [21] studied 247 pediatric admissions for DKA for the presence of infections. They found a low yield of positive blood culture results in children who had bacterial infections (3.2%) and positive urine cultures (1.2%). Our findings reiterate the importance of existing recommendations regarding using clinical judgments in ordering these tests. We found that upon presentation, the patients who did not require any fluid bolus were approximately half of the total (181/373, 48%) differentiating it from other reports [19]. This fact may be attributed to the milder presentation.

In conclusion, this study found notable findings in many characteristics, such as, higher mean age of presentation (age group: 10-14 years), high rate of non-compliance to insulin as the cause of precipitation (67% of DKA episodes in diagnosed diabetics), and a high prevalence of abdominal pain (69%) at presentation. Trends of correction of metabolic profile in the time frame of 0-6 hours and 6-12 hours showed blood glucose, PH, anion gap, serum osmolality, serum potassium, and serum phosphate changes to be most prominent during the initial 6 hours of management, while trends of serum bicarbonate and blood urea nitrogen demonstrated predominant change in the initial 12 hours of management. We consider that these findings should open the venue for further comparative studies. In the future all the characteristics should be individually explored and thoroughly compared to the previous literature from other global geographic areas. Overall, provisions of awareness to clinicians regarding these findings shall help improve care of pediatric DKA patients.

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