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Incidence and risk factors of acute kidney injury in pediatric diabetic ketoacidosis: A retrospective study

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ABSTRACT

One of the typical complications of diabetic ketoacidosis (DKA) is acute kidney injury (AKI) in pediatric patients. However, the incidence and AKI's risk factors in pediatric patients with DKA remain elusive in Saudi Arabia. We investigated the occurrence rate and associated risk factors of AKI among pediatric DKA patients in Saudi Arabia. A single-center observational retrospective cohort study was conducted at the Maternity and Children Hospital in Buraydah, Saudi Arabia between August 2019 and August 2021. There were 207 DKA patients, including 74 (35.7%) patients with AKI. Among AKI patients, 65 (87.8%) patients presented with stage 1 and 9 (12.1%) patients presented with stage 2 AKI. In patients with DKA, aging, hyperglycemia, increased heart rate, elevated WBC count and serum creatinine, decreased pH and HbA1c were risk factors for AKI. Altogether, the severity of AKI is influenced by several risk factors in DKA patients. Hence, there is an urgent need for conducting prospective long-term research to better comprehend the risk factors and longstanding complications of AKI.

Keywords: diabetic ketoacidosis, acute kidney injury, prevalence, risk factors, pediatric population

1. INTRODUCTION

Diabetic ketoacidosis (DKA) is considered as a fatal complication in children suffering from type 1 diabetes mellitus (T1DM) due to critical clinical and metabolic derangements (Orban et al., 2014; Aljuhani et al., 2021). DKA may be an initial presentation of recently diagnosed TIDM or in cases of insulin omission in previously diagnosed children (Hursh et al., 2017). It is the primary reason for mortality, hospitalization and sickness, in pediatric TIDM patients (Razav, 2010; Realson et al., 2012). Interestingly, the prevalence of DKA at the beginning of diabetes mellitus changes significantly among various geographical regions with a high prevalence reported in developing

countries (Razav, 2010). These patients exhibit insulin insufficiency, which leads to DKA, described by severe dehydration and other symptoms like osmotic diuresis, hyperglycemia, metabolic ketoacidosis, etc. (Hursh et al., 2017). Pediatric patients are more vulnerable to a complication like volume depletion than adults because compensatory mechanisms are not yet well developed (Jefferies et al., 2015). Volume depletion or prerenal disease is the most typical risk factor for the creation of acute kidney injury (AKI) (Huang et al., 2020), a state marked by compromised renal function, reduced eradication of waste products, dysregulated electrolyte and acid-base balance and compromised fluid homeostasis (Sutherland et al., 2015).

Besides, AKI is risk created independently associated for death with higher mortality rates in children (Uber & Sutherland, 2020). AKI is also correlated to the risk of developing chronic kidney disease in adulthood, mainly in patients with recurrence (Myers et al., 2020). Furthermore, elevated serum urea nitrogen, a significant finding in AKI patients, is a well-known risk factor for developing cerebral edema (Glaser et al., 2001), a common etiology of illness and mortality in DKA patients. Pediatric-specific DKA protocols were developed to lessen the risk of cerebral edema (Hursh et al., 2017), which warrants further research about the contributing factors to AKI development in DKA patients.

This study seeks to evaluate the occurrence frequency of AKI in children with DKA and to identify the associated clinical and biochemical risk factors. Recent research has demonstrated a high occurrence of AKI in kids suffering from DKA, (Orban et al., 2014; Hursh et al., 2017; Huang et al., 2020; Myers et al., 2020; Yunos et al., 2012; Chen et al., 2020). A 2020 retrospective study conducted at Mackay Children's Hospital included 301 episodes of DKA. Among those 170 (56.5%) had AKI during admission, with 31.8% (54/170) had severe cases of AKI (Huang et al., 2020). Another research was performed in British Columbia, Canada at a tertiary children hospital. In this study, 106 (64.2%) out of a total of 165 kids having DKA were later hospitalized for subsequently got AKI, including 37 (34.9%) with stage 1, 48 (45.3%) with stage 2 and 21 (19.8%) with stage 3 AKI. Two children required hemodialysis to offset oliguria and fluid overload during hospitalization. Additionally, 105 (99.1%) of 106 children got AKI within the first day after they were hospitalized and by the end of the 72 hours, By three days of hospitalization the maximum documented AKI stage was reached, only 54 (50.9%) patients had a verifiable treatment of their AKI. Furthermore, four more cases (3.8%) had verifiable resolution within ninety-six hours (Hursh et al., 2017).

In addition, a 2014 retrospective study by Jean-Christophe Orban included 94 ICU admissions with DKA. Among those, 47 patients (50%) had AKI on admission according to RIFLE criteria. At 12 hours, the proportion of patients with AKI reduced to 21. After 24 hours, only 13 patients still had AKI (Orban et al., 2014). Another retrospective research was performed at a single Korean center that incorporated ninety episodes of DKA in fifty-eight kids suffering from type 1 diabetes mellitus. 70 hospitalizations (77.8%) of 44 children had AKI on admission. Stage 1 AKI occurred in 18 episodes (20.0%), stage 2 AKI in 39 (43.3%), while stage 3 AKI occurred in 13 episodes (14.4%). After 12 hours, the number of AKI patients was reduced 28 (47.4%), while after 24 hours of admission, it was further reduced to 13 (28.3%) (Yang et al., 2021) AKI in pediatrics can present between a minimal elevations in blood creatinine levels to anuric renal failure necessitating renal dialysis (Hursh et al., 2017). Nevertheless, multiple clinical and biochemical markers are linked to the development and severity of AKI. Children suffering with AKI exhibit lower pH and bicarbonate values. Severe cases of AKI have a significant increase in heart rate, serum potassium, blood urea nitrogen and corrected serum sodium and blood glucose levels. These biochemical markers reflect the volume depletion in the creation of AKI and its severity in children with DKA (Huang et al., 2020).

2. MATERIALS AND METHODS

This research study is characterized by a cohort in a single center and is observational retrospective. Moreover, it is performed at the Maternity and Children Hospital in Buraydah, Saudi Arabia. The study recruited patients admitted between August 2019 and August 2021. We included all patients younger than 14 years old with documented DKA. Patients with incomplete clinical documentation and type 2 Diabetes mellitus were excluded. Data collection took place from December 30 to March 30, 2022.

The guidelines and protocols of the Saudi ministry of health for diabetes emergencies were the primary treatment protocol for treating patients in the recruited population (Zubair et al., 2018). We collected data about age, gender, BMI, date of Diagnosis for diabetes mellitus type 1, aggravating factors of DKA and duration. We also measured the length of hospital stay, clinical outcomes, and associated comorbidities. Additionally, vital signs, arterial blood gases, complete blood count and electrolytes were also recorded. The data was collected from the clinical notes and records of the Maternity and Children Hospital in Buraydah.The guidelines and protocols of the Saudi ministry of health for diabetes emergencies define DKA as presentation of Hyperglycemia (blood glucose >11mmol/L ≈ 200mg/dL), glycosuria, metabolic acidosis (Venous pH <7.3 or bicarbonate <15mmol/L) with ketonemia or ketonuria (Zubair et al., 2018).

The Clinical Practice Guidelines for the Kidney Disease/Improving Global Outcomes (KDIGO) in case of AKI that is specified as an increase in serum creatinine up to 1.5 times the baseline. We also divided the AKI patients into three categories based on the severity of AKI according to KDIGO criteria. These included stage 1 AKI is patients with creatinine 1.5.-1.9 times the normal baseline, stage 2 AKI with creatinine 2.0 – 2.9 times the normal and stage 3 AKI with creatinine three or more times the normal range (Sutherland et al., 2015). Since we did not have data about 24 h urine collections and baseline creatinine levels before their admission, we calculated an expected baseline serum creatinine level using the estimation equation by Schwartz (eGFR = k * L in cm/Scr; K is 0.45 for term infant, 0.55 for children and adolescent girls and 0.7 for teenage boys) (15), using an expected GFR of 120mL/min/1.73 m2 according to previously established levels for patients without a prior baseline (Zappitelli et al., 2008; Basu et al., 2015).

All data was analyzed using the IBM SPSS, v 24 statistics software. We utilized descriptive statistics methods using continuous variables. These continuous variables include range and median as well as the categorical variables, which are proportions and frequency. Furthermore, we tested the statistical significance among various groups in the cohort by employing well-known statistical tests like Fisher exact test and χ2-test. We utilized the independent t-test for continuous variables and utilized logistic regression to determine the deductible-associated factors. We set the value of statistical significance as P-value <0.05. An ethical consent was acquired from the Qassim Region Research Ethics Committee (QREC) with the following Ethical approval code 1443-830910. We warranted the anonymity and the protection of the privacy of the participants of this study.

3. RESULTS

The study was based on 231 episodes of pediatric DKA patients hospitalized at the Maternity and Children Hospital in Buraydah, Saudi Arabia, from January 1st 2020, to December 31st 2021. From these episodes, 207 met our inclusion criteria and 24 were excluded; 8 episodes had missing medical records and 16 had incomplete data sets. Data collection took place from December 30 until March 30, 2022. Among the DKA patients, 74 (35.74%) had AKI and 133 (64.26%) had no AKI. Among AKI patients 65 (87.8%) presented with stage 1 AKI and 9 (12.1%) presented stage 2 AKI, according to the KDIGO guidelines (Sutherland et al., 2015). Baseline biological and clinical characteristicsof the patient group with a focus on renal function are reported in Tables 1 and 2 and Figure 1. Among 207 patients, 73 (35.3%) were males, and 134 (64.7%) were females. The patients with AKI stage 1 included 26 (40.0%) males and 39 (60.0%) females.

Patients with AKI stage 2 had 5 (55.6%) males and 4 (44.4%) females. The non-AKI patients included 42 (31.3%) males, and 92 (68.6%) females. Age (median + years) of the AKI group 1 patients was 11.01 (4.0-14.0), AKI group 2 patients was 10.22 (1.0-14.0), and non-AKI patients was 9.6 (0.8-15.0). The resulting data showed that most of the AKI patients were females. However, the higher number of females participated in this study and AKI incidence increased when advancing age. Our findings demonstrate that AKI stage 1 and 2 patients had lower pH {7.06(6.8-7.3), 7.04 (6.83-7.17)} and HbA1c levels {11.28(8.00-19.83), 11.04 (8.9-14.0)} and greater heart rates {(114.64±18.89) (128.88±31.52)}, blood glucose {531.86(200–817.3), 535.786(229.0-750.0)}, serum creatinine {73.50(60.0-112.0), 103.889(91.0-112.0)} and WBCs {18.50(5.84-51.68), 26.43(11.28-51.68)} than non-AKI patients (Tables 1 and 2 and Figure 1). Conversely, other factors including BMI, length of stay, presence of comorbidities, clinical outcomes, date of diagnosis of type 1 DM DKA precipitating factors, systolic and diastolic blood pressure (mmHg), body temperature, plasma sodium, potassium, phosphate, chloride, HCO_3, lactate, CO_2, O_2 saturation, hematocrit, hemoglobin, platelets, BUN, serum ketone and estimated creatinine were not signified as main risk factors to create AKI in DKA patients.

Table 1 Baseline Demographical and clinical traits of the patient group.

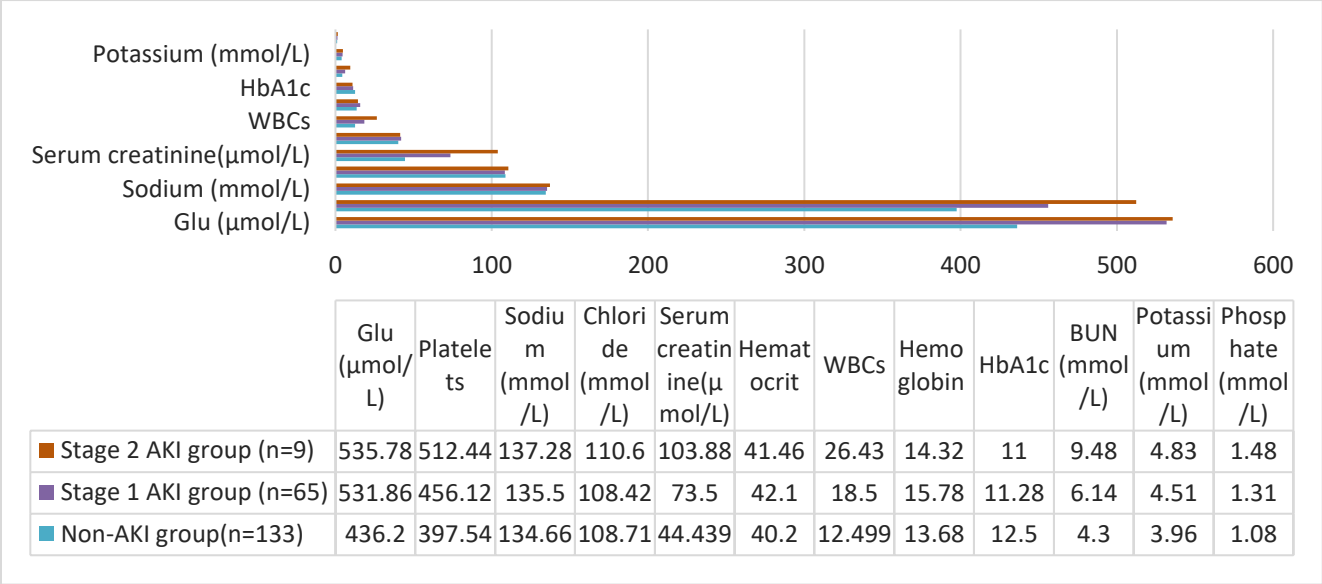
Parameters	Total (n = 207)	Non-AKI group (n = 133)	Stage 1 AKI group (n = 65)	Stage 2 AKI group (n = 9)	p
Gender					
Male (n, %)	73 (35.0)	42 (31.3)	26 (40.0)	5 (55.6)	0.31
Female (n, %)	134 (64.7)	92 (68.6)	39 (60.0)	4 (44.4)	0.74
Age (mean and years)	10.129 (0.8-15)	9.6 (0.8-15.0)	11.1 (4.0-14.0)	10.22 (1.0-14.0)	0.053
BMI (kg/m2)	18.08 (7.52-65.01)	18.16 (8.0-65.0)	17.46 (7.52-31.25)	19.29 (11.11-36.0)	0.98
Length of stay (days)					0.53
0-4	57 (27.5)	104 (78.1)	54 (83.0)	6 (66.6)	

4-8	38 (18.3)	28 (21.0)	9 (13.8)	1 (11.1)	
8-12	6 (2.89)	0 (0)	2 (3.07)	2 (22.2)	
12-16	1(0.4)	1(0.8)	0 (0)	0 (0)	
Comorbidities					
N/A	195 (94.3)	126 (94.7)	62 (95.4)	9 (100)	0.086
Other	12 (5.7)	7 (5.3)	3 (4.6)	0 (0)	
Clinical outcomes					
Recovered	204 (98.6)	130 (97.7)	65 (100)	9 (100)	0.62
Unknown	3 (1.4)	3 (2.3)	0 (0)	0 (0)	
DKA precipitating factors					
Insulin Omission	59 (28.5)	44 (33.0)	21 (32.3)	3 (33.3)	
Newly diagnosed	56 (27.1)	41 (30.8)	20 (30.7)	2 (22.2)	0.084
No precipitating factor	29 (14.0)	16 (12.0)	12 (18.4)	2 (22.2)	
others	63 (30.4)	32 (24.0)	9 (13.8)	2 (22.2)	

Table 2 Baseline biological and laboratory traits of the patient group with a focus on renal function.

Parameters	Total (n=207)	Non-AKI group(n=133)	Stage 1 AKI group (n=65)	Stage 2 AKI group (n=9)	p
Vital signs during ER presentation					
Systolic blood pressure (mmHg)	108.93 ± 14.678	107.99 ± 14.068	111.36 ± 16.32	108.77 ± 9.85	0.276
Diastolic blood pressure- (mmHg)	66.10 ± 10.903	65.045 ± 11.450	68.29 ± 9.85	66.00 ± 12.38	0.333
Temperature(°C)	36.84 (36.0–38.2)	36.79 (36.0–37.9)	36.91 (36.0-38.2)	37.2 (36.5-38.2)	0.106
Heart rate (times/min)	110.35 ± 17.719	108.174 ± 15.704	114.64 ± 18.89)	128.88 ± 31.52	0.045
O_2 Sat (%)	97.54 ± 1.599	97.50 ± 1.67	97.66 ± 1.40	97.44 ± 2.12	0.73
ABG during ER					
pH	7.12 (6.7-7.7)	7.15 (6.7–7.7)	7.06 (6.80-7.31)	7.04 (6.83-7.17)	0.046
HCO_3	9.49 (2.3-37.0)	10.15 (2.3-37.0)	8.0 3(2.5-34.0)	9.033 (3.7-34.0)	0.67
Lactate	141 (68.1)	71 (53.4)	36 (55.4)	4(44.4)	0.88
N/A	66 (31.9)	62 (46.6)	29 (44.6)	5 (55.6)	
CO_2	24.4 (1.13-63.0)	25.03 (1.13-63.0)	23.49 (3.3-43.0)	20.88 (13.0-26.0)	0.684
CBC, chemistry during ER					
Glu (μmol/L)	471.44(54.0-817.38)	436.2 8 (54.0-774.00)	531.86 (200.0-817.3)	535.78 6(229.0-750.0)	0.038
HbA1c	12.8 (11.1–14.5)	12.5 (10.6–14.7)	11.28 (8.00-19.83)	11.0 4(8.9-14.0)	<0.02
Serum creatinine(μmol/L)	56.01 (21.0-112.0)	44.439 (21.0-59.0)	73.50 (60.0-112.0)	103.88 9(91.0-112.0)	0.038
WBCs	14.88 (4.90-51.68)	12.499 (4.90–48.54)	18.50 (5.84-51.6)	26.43 (11.82-51.68)	<0.001

Hematocrit	40.91 (7.88-53.30)	40.2 9(28.9-48.0)	42.1 0(7.88-53.30)	41.46 (33.1-53.3)	0.067
Hemoglobin	14.36 (8.7-16.5)	13.68 (10.6-15.5)	15.78 (8.7-105.0)	14.32 (10.5-15.5)	0.079
Platelets	420.86 (4.8-945.0)	397.54 (4.8-782.0)	456.12 (27.0-945.0)	512.44 (315.0-691.0)	0.25
Sodium (mmol/L)	134.91(13.45-154.95)	134.66(13.45-147.6)	135.5 6(123.0-154.95)	137.28 (130-145.11)	0.51
Chloride (mmol/L)	108.38(16–134.37)	108.71(85.0-127.01)	108.42 (16.0-134.37)	110. 6(86.0-134.37)	0.078
BUN (mmol/L)	5.13 (1.10-13.20)	4.3 (1.10–8.80)	6.14 (2.90-12.60)	9.48 (4.60-13.20)	0.064
Phosphate (mmol/L)	1.17 (0.30-4.11)	1.08 (0.30–2.52)	1.31 (0.39-4.11)	1.48 (0.86-2.08)	0.096
Potassium (mmol/L)	4.17 (1.32-6.40)	3.96 (1.32–6.31)	4.51 (2.80-6.40)	4.83 (3.19-5.80)	0.563



	Glu (µmol/L)	Platelets	Sodium (mmol/L)	Chloride (mmol/L)	Serum creatinine(µmol/L)	Hematocrit	WBCs	Hemoglobin	HbA1c	BUN (mmol/L)	Potassium (mmol/L)	Phosphate (mmol/L)
Stage 2 AKI group (n=9)	535.78	512.44	137.28	110.6	103.88	41.46	26.43	14.32	11	9.48	4.83	1.48
Stage 1 AKI group (n=65)	531.86	456.12	135.5	108.42	73.5	42.1	18.5	15.78	11.28	6.14	4.51	1.31
Non-AKI group(n=133)	436.2	397.54	134.66	108.71	44.439	40.2	12.499	13.68	12.5	4.3	3.96	1.08

Figure 1 Bar graph laboratory traits of the patient group in comparison to AKI group

The results of the multivariate logistic regression showed that older age [OR (95% CI) 9.99 (9.503-10.487), P=0.034] along with, increased Glucose [OR (95% CI), 474.019(452.295-495.743) P = 0.001], heart rate [OR (95% CI) 110.60 (108.08-113.12), P = 0.045], serum creatinine [OR (95% CI) 56.199 (53.459-58.938), P = 0.054], WBCs [OR (95% CI) 14.984 (13.692-16.277), P = 0.043] and reduced pH 7.125 (7.104-7.146), P = 0.051 and HbA1c [OR (95% CI) 11.12 (11.0-11.89), P = 0.034] were designated as risk factors for developing AKI in DKA patients (table 3). The remaining variables, including gender, systolic and diastolic blood pressure, body temperature, sodium, potassium, phosphate, chloride, HCO_3, lactate, CO_2, hematocrit, hemoglobin, platelets, BUN and serum ketone, were not the risk factors to develop AKI. Univariate evaluation of gender [male 1.764 (0.982–3.165) P = 0.154, female 1.814 (0.995-4.522) P = 0.166], age 10.104 (9.630-10.579) P = 0.038, BMI 18.085 (17.20-18.96) P = 0.897, length of stay 3.099 (2.79-3.40) P = 0.356, comorbidities 1.58 (0.12-1.97) P = 0.851, clinical outcomes 2.29 (1.62-2.84) P = 0.096, DBP 66.077 (64.586–67.569) P = 0.169, SBP 108.879 (106.870–110.888), P = 0.234, body temperature 36.8411 (36.794–36.888), P = 0.632, heart rate 110.309 (107.885-112.733), P = 0.001, DKA precipitating factors 3.45 (1.76-3.89), P = 0.681, O_2 saturation 97.545 (97.327-97.765) P = 0.081, pH 7.125 (7.105-7.146) P = 0.001, HCO_3 9.493 (8.70-10.27) P = 0.072, lactate 2.343 (0.0-6.34) P = 0.649, CO_2 24.47 (23.40-25.45) P = 0.981, glucose 471.286 (450.41–492.16) P = 0.032, serum creatinine 55.908 (53.277-58.539) P = 0.004, WBCs 14.855 (13.614-16.096) P = 0.054, hematocrit 40.91 (40.31-41.51) P = 0.981, hemoglobin 14.36 (13.47-15.24) P = 0.079, platelets 420.86 (402.64-439.09) P = 0.582, phosphate 1.176 (1.111–1.242) P = 0.081, sodium 134.902 (133.55-136.24), P = 0.068, chloride 108.385 (106.90-109.86) P = 0.095, potassium 4.175 (4.074-4.276), P = 0.497, BUN 5.121 (4.834-5.409), P = 0.613, HbA1c 12.8 (11.1–14.5) P = 0.049, serum ketone 0.23 (0.1-0.8) P = 0.083 (Table 3).

Table 3 Risk factors of AKI in DKA patients

Parameters	Logistic analysis	p		p
	Univariate analysis		Multivariate analysis	
	OR (95%CL)		OR (95%CL)	
Gender				
Male	1.764 (0.982–3.165)	0.154		
Female	1.814 (0.995-4.522)	0.166		
Age	10.104 (9.630-10.579)	0.038	9.99 (9.503-10.487)	0.034
BMI (kg/m2)	18.085 (17.20-18.96)	0.897		
Length of stay(days)	3.099 (2.79-3.40)	0.356		
Comorbidities	1.58 (0.12-1.97)	0.851		
DKA precipitating factors	3.45 (1.76-3.89)	0.681		
Vital signs during ER presentation				
SBP (mmHg)	108.879 (106.870–110.888)	0.234		
DBP (mmHg)	66.077 (64.586–67.569)	0.169		
Temperature (°C)	36.8411 (36.794–36.888)	0.632		
Heart rate (times/min)	110.309 (107.885-112.733)	0.001	110.60 (108.08-113.12)	0.045
O_2 Sat (%)	97.545 (97.327-97.765)	0.081		
ABG during ER				
PH	7.125 (7.105-7.146)	0.001	7.125 (7.104-7.146)	0.051
HCO_3	9.493 (8.70-10.27)	0.072		
Lactate	2.343 (0.0-6.34)	0.649		
CO_2	24.47 (23.40-25.45)	0.981		
CBC, chemistry during ER				
Glucose (μmol/L)	471.286 (450.41–492.16)	0.032	474.019 (452.295-495.743)	0.001
Serum Creatinine(μmol/L)	55.908 (53.277-58.539)	0.004	56.199 (53.459-58.938)	0.054
WBCs (109/L)	14.855 (13.614-16.096)	0.054	14.984 (13.692-16.277)	0.043
Hematocrit	40.91 (40.31-41.51)	0.981		
Hemoglobin	14.36 (13.47-15.24)	0.079		
Platelets	420.86 (402.64-439.09)	0.582		
Phosphate	1.176 (1.111–1.242)	0.081		
Sodium	134.902 (133.55-136.24)	0.068		
Chloride	108.385 (106.90-109.86)	0.095		
Potassium	4.175 (4.074-4.276)	0.497		
BUN	5.121 (4.834-5.409)	0.613		
HbA1c	12.8 (11.1–14.5)	0.049	11.12 (11.0-11.89)	0.034
Serum Ketone	0.23 (0.1-0.8)	0.083		

Multiple regression was conducted to measure the AKI prediction values, including age, BMI, pH, HCO_3, lactate, sodium, potassium, phosphate, chloride, WBCs, glucose, HbA1c in patients with DKA. The results from multiple regression by using serum creatinine as a variable showed a 95% CI odd ratio values of: Age (1.54-2.78) (p = 0.047), BMI (-4.01-2.18) (p = 0.982), pH (-36.71-2.58) (p = 0.024), HCO_3 (-7.63-1.74) (p = 0.217), lactate (0.42-0.98) (p = 0.345), WBCs (0.168-0.738) (p = 0.082), chloride (-0.336-0.065) (p = 0.184), potassium (5.486-11.805) (p = 0.450), sodium (-0.292-0.130) (p = 0.390), phosphate (-2.271-7.148) (p = 0.981), glucose (-0.002-0.028) (p = 0.057), HbA1c (0.45-10.68) (p = 0.953) (Table 4).

Table 4 AKI prediction value on patients with DKA using multiple regressions

Variable	Odds ratio (95% CI)	P value
Age (Years)	(1.54-2.78)	0.047
BMI (Kg/m2)	(-4.01-2.18)	0.982
pH	(-36.71-2.58)	0.024
HCO_3	(-7.63-1.74)	0.217
Lactate	(0.42-0.98)	0.345
WBC	(0.168-0.738)	0.082
Chloride	(-0.336-0.065)	0.184
Potassium	(5.486-11.805)	0.450
Sodium	(-0.292-0.130)	0.390
Phosphate	(-2.271-7.148)	0.981
Glucose	(-0.002-0.028)	0.057
HbA1c	(0.45-10.68)	0.953

4. DISCUSSION

The global prevalence of DM has progressively increased and DM is a critical pathophysiological factor for CKD and several chronic noncommunicable disorders (Zhang et al., 2013). DKA is a severe consequence of DM that requires prompt treatment to prevent mortality and morbidity (Orban et al., 2014). AKI is a frequent consequence of DKA and is linked to poor short-term prognosis in patients with DKA (Orban et al., 2014; Hursh et al., 2017). Additionally, elevated plasma creatinine is a common finding in hyperglycemic crises and is more noticeable in hyperglycemic hyperosmolar conditions than in DKA (Balaji et al., 2018; Barski et al., 2012). This may partly be because the metabolic acidosis reduces kidney blood flow in healthy participants, while concomitantly increasing the release of inflammatory mediators. It was recently demonstrated that metabolic acidosis worsens ischemia/reperfusion-induced AKI. However, there is limited evidence that metabolic acidosis contributes to the onset of AKI (Barski et al., 2012).

In our study, 74 (35.74%) of the DKA admissions suffered from AKI various studies have found a wide range of prevalence rates of AKI in children admitted with DKA (Wagner et al., 1999; Hursh et al., 2017). For example, the reported incidence was as high as (77.8%) in a Korean single-center study (Yang et al., 2021). Additionally, 50% of adults hospitalized for DKA in a study matched the RIFLE criteria for AKI (Orban et al., 2014). Furthermore, AKI was prevalent in 64.3% of the 165 children with DKA studied, which used KDIGO guidelines as the criteria to diagnose AKI (Hursh et al., 2017). Both studies demonstrate that a high percentage of patients admitted for DKA developed AKI. However, lower trends in the incidence of AKI are also reported in the literature, which are similar to our finding. The incidence of AKI in infants with DKA in an Indian study was only 35.4% (Balaji et al., 2018). Similarly, in a retrospective studyonly 30% of kids with DKA brought and admitted in the PICU had AKI, which are consistent with our finding. Our study seems to be at the lower end of incidence compared with most of the literature as well as in severity given that we had no stage 3 AKI episodes following the KDIGO criteria.

Our study specifies the occurrence of AKI in children with DKA, along with their associated clinical and biochemical risk factors. AKI patients are older in our study. For example, AKI stage 1 and stage 2 patients had higher mean for age than non-AKI group, so age is likely a contributing factor for a longer duration DM disease and compromised renal function in the long-term. This may help to partially explain the rise of AKI in older age groups, which is in agreement with the reports of reduced renal function with advancing age (Glaser et al., 2001). Interestingly, a previous study conducted at the hospital of Sun Yat-sen Memorial showed a similar finding, in which older age patients were significantly identified with a higher incidence of AKI (Chen et al., 2020). We have found that there was higher heart rates in AKI patients in comparison to the non-AKI group, which is reported in another

study conducted in Mexico, where beats/minute were found to be 122.58 compared to 111.8, while p=0.079 (García et al., 2020). The count of White Blood Cells (WBCs) was observed as more in the group with AKI, similar to the elevated level reported in another study carried out by Yang EM in Korea (Yang et al., 2021). Additionally, we found that AKI patients presented with a higher blood glucose level in comparison to non-AKI patients, which is consistent with the literature (Huang et al., 2020; Chen et al., 2020; García et al., 2020).

Furthermore, the AKI group demonstrated a lower level of pH, which agrees with previous findings of a reduced pH as a risk factor for developing AKI in a patient with DKA (Huang et al., 2020; Chen et al., 2020; Yang et al., 2021). Moreover, in a study conducted at the Children's Hospital in British Columbia, they found that low level of pH and bicarbonate was highly associated with severity of AKI (Hursh et al., 2017). Also, our study showed that AKI occurred more in DKA patients with reduced HbA1c, whereas a study from Korea demonstrated no difference between the two groups (Orban et al., 2014). Ultimately, we demonstrate that AKI is accompanied with higher levels of glucose greater heart rates, serum creatinine and WBCs with lesser pH and HbAlc values compared to the patients without AKI (Uchino et al., 2010). While other factors include BMI, length of stay, comorbidities, clinical outcomes, date of diagnosis of type 1 DM, DKA precipitating factors, systolic and diastolic blood pressure, body temperature, sodium, potassium, phosphate, chloride, HCO_3, lactate, CO_2, O_2 Sat, hematocrit, hemoglobin, platelets, BUN, serum ketone and estimated creatinine have no overall effect on the AKI patients (Tables 1 and 2 and Figure 1).

AKI patients had greater blood glucose levels when admitted to the hospitals, despite having the same disease severity based on their acid-base status. The two causes listed below at least partially account for this outcome. First, in critically sick patients, AKI appears to be linked with insulin resistance and inflammation (Mehta, 2007; Basi et al., 2005). Second, reduced glycosuria, a practical approach to controlling hyperglycemia, may be linked to kidney failure. The kidneys entirely reabsorb blood glucose at physiological levels. The sodium-glucose linked transporter (SGLT) 1 and 2 are the significant cotransporters involved in this process, which occurs concurrently with sodium absorption. Diabetes causes SGLT 1 and 2 to absorb glucose more readily (Vallon & Thomson, 2012). However, glycosuria regulates hyperglycemia when it rises above the threshold level for glucose reabsorption. Renal perfusion is impaired in AKI patients, which may help reduce glucose urine losses and thwart hyperglycemia (Adrogue et al., 1982).

The impact of hyperchloremia on kidney function has recently come to light (Yunos et al., 2012). However, we could not differentiate between AKI and non-AKI patients in terms of serum chloride in our population, so this relationship was not found in our study (Rocktaeschel et al., 2003). Further, AKI and DKA patients usually present with hyperphosphatemia (Fisher & Kitabchi, 1983). Specifically, insulin shortage in DKA results in intracellular to extracellular changes, whereas in AKI, decreased renal perfusion causes hyperphosphatemia. These findings may account for the AKI patients receiving more insulin and improving renal function. Therefore, patients will still require supplementation even if their serum phosphate levels are higher. Age, blood sugar, WBCs, PH, serum creatinine, heart rate and HbA1c are some factors with risk of having severe DKA, signified in this research study. These parameters are not prognostic indicators or part of the various DKA severity levels in clinical practice. However, they might make it easier to consider the unique characteristics of AKI patients in this situation. The first step in treating AKI is to rectify hypovolemia by infusing fluids (Bellomo et al., 2004; Brochard et al., 2010). However, excessive fluid infusion, particularly in the event of oliguria, might result in additional complications. Furthermore, the ICU is the best place to provide the more intensive care and intrusive monitoring that these patients require.

Study Limitations

This was a single-center study. However, it is the referral center for the whole region and the only pediatrics hospital at the city. Second, no study participants had 24h urine collections or baseline creatinine values before their admission so that detailed urine output data was unavailable. Thus, we decided not to employ urine output criteria in this study to diagnose AKI and instead relied on estimates calculation which was the most common used methodology in the literature for similar studies.

5. CONCLUSION

A serious complication of DKA, AKI was found to be influenced by age, Glu, WBCs, heart rate, serum creatinine levels, HbA1c and pH. There were 74 (35.7%) patients had AKI; 65 (87.8%) had stage 1 symptoms, 9 (12.6%) had stage 2 presentations. The prevention of kidney function impairment in DKA sufferers with AKI requires regular follow-up in addition to early detection and treatment of AKI in hospitals. There is an urgent need for prospective long-term research to better comprehend the long-lasting complications and the corresponding risk factors related to AKI in the cohort, mainly as young kids with diabetes mellitus are at peril of getting the long-lasting kidney illness and a life-long diabetic nephropathy on secondary level.

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Authors' contribution

Dr. Abdullah AlDamigh- Overall supervision and guidance of the entire research process, from topic selection to the finalization of conclusion writing.

Dr. Husam AlAhmadi- He has aided and contributed immensely to the access to data, data collection, analysis and writings related to results

Abdullah AlHojailan - Contributed to the entire process from topic selection, to Review of literature, study design, data collection, Data management and analysis, progress report, data analysis, final report and manuscript writing, and guidance of the writing process and progression.

Emad AlFadhel - Was mainly responsible for the construction of the methodology, data collection and management and analysis of the data with writing parts related.

Mohammad AlKhattaf - He had major contribution in extracting the results and writing the discussion, along with the collection and management of data.

Fatimah Almeathem- She was responsible mainly for the construction of the introduction, along with language editing and data collection and its management.

Ibrahim Algosair- Contributed to many parts in a major way, from constructing the methodology, doing the review of literature, analyzing the data and extracting results and findings from it along with data collection and management.

Ghadah AlHarbi- She was responsible for the construction of the initial parts of the study along with writing the introduction and literature review, contributed to the collection of data and its management along with editing other parts

Abdullah AlSamani- He contributed mainly to the writing of results and the discussion over it along with reviewing the literature, and collecting and managing the data.

Ethical approval

The study was approved by Qassim Region Research Ethics Committee (QREC) (Ethical approval code 1443-830910).

Informed consent

Not applicable.

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

REFERENCES AND NOTES

1. Adrogué HJ, Wilson H, Boyd AE, Suki WN, Eknoyan G. Plasma acid-base patterns in diabetic ketoacidosis. N Engl J Med 1982; 307(26):1603–1610. doi: 10.1056/NEJM198212233072603
2. Aljuhani NR, Alamoudi NM, Majali NB, Algouzi RM, Alzubaidi FA, Alnajri SM. Characteristics and outcome of severe diabetic ketoacidosis in East Jeddah Hospital, Saudi Arabia. Medical Science, 2021, 25(112),1407-1412
3. Balaji M, Jayashree M, Nallasamy K, Singhi S, Bansal A. Predictors and Outcome of Acute Kidney Injury in Children with Diabetic Ketoacidosis. Indian Pediatr 2018; 55(4):311–314.
4. Barski L, Nevzorov R, Rabaev E, Jotkowitz A, Harman-Boehm I, Zektser M, Zeller L, Shleyfer E, Almog Y. Diabetic ketoacidosis: Clinical characteristics, precipitating factors, and outcomes of care. Isr Med Assoc J 2012; 14(5):299–303.

5. Basi S, Pupim LB, Simmons EM, Sezer MT, Shyr Y, Freedman S, Chertow GM, Mehta RL, Paganini E, Himmelfarb J, Ikizler TA. Insulin resistance in critically ill patients with acute renal failure. Am J Physiol Renal Physiol 2005; 289(2):F259-264. doi: 10.1152/ajprenal.00002.2005
6. Basu RK, Kaddourah A, Terrell T, Mottes T, Arnold P, Jacobs J, Andringa J, Goldstein SL. Assessment of Worldwide Acute Kidney Injury. Renal Angina and Epidemiology in critically ill children (AWARE): Study protocol for a prospective observational study. BMC Nephrol 2015; 16:24. doi: 10.1186/s12882-015-0016-6
7. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute Dialysis Quality Initiative workgroup. Acute renal failure-definition, outcome measures, animal models, fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care Lond Engl 2004; 8(4):R204-212. doi: 10.1186/cc2872
8. Brochard L, Abroug F, Brenner M, Broccard AF, Danner RL, Ferrer M, Laghi F, Magder S, Papazian L, Pelosi P, Polderman KH.An Official ATS/ERS/ESICM/SCCM/SRLF Statement: Prevention and Management of Acute Renal Failure in the ICU Patient: An international consensus conference in intensive care medicine. Am J Respir Crit Care Med 2010; 181(10):1128–1155. doi: 10.1164/rccm.200711-1664ST
9. Chen J, Zeng H, Ouyang X, Zhu M, Huang Q, Yu W, Ling L, Lan H, Xu A, Tang Y. The incidence, risk factors and long-term outcomes of acute kidney injury in hospitalized diabetic ketoacidosis patients. BMC Nephrol 2020; 21(1):48. doi: 10.1186/s12882-020-1709-z
10. Fisher JN, Kitabchi AE. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosi. J Clin Endocrinol Metab1983; 57(1):177–180. doi: 10.1210/jcem-57-1-177
11. García SS, Castellanos MB, Morales AV. Acute kidney injury and diabetic ketoacidosis in pediatric patients: Risk factors. Arch Argent Pediatr 2020; 118(2):135-138.
12. Glaser N, Barnett P, McCaslin I, Nelson D, Trainor J, Louie J, Kaufman F, Quayle K, Roback M, Malley R, Kuppermann N. 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. doi: 10.1056/NEJM200101253440404
13. Himmelfarb J, Joannidis M, Molitoris B, Schietz M, Okusa MD, Warnock D, Laghi F, Goldstein SL, Prielipp R, Parikh CR, Pannu N, Lobo SM, Shah S, D'Intini V, Kellum JA. Evaluation and initial management of acute kidney injury. Clin J Am Soc Nephrol 2008; 3(4):962–967. doi: 10.2215/CJN.04971107
14. Huang SK, Huang CY, Lin CH, Cheng BW, Chiang YT, Lee YC, Yeh SN, Chan CI, Chua WK, Lee YJ, Ting WH. Acute kidney injury is a common complication in children and adolescents hospitalized for diabetic ketoacidosis. Plo S One 2020; 15(10):e0239160. doi: 10.1371/journal.pone.0239160
15. Hursh BE, Ronsley R, Islam N, Mammen C, Panagiotopoulos C. Acute Kidney Injury in Children with Type 1 Diabetes Hospitalized for Diabetic Ketoacidosis. JAMA Pediatr 2017; 171(5):e170020. doi: 10.1001/jamapediatrics.2017.0020
16. Jefferies CA, Nakhla M, Derraik JGB, Gunn AJ, Daneman D, Cutfield WS. Preventing Diabetic Ketoacidosis. Pediatr Clin North Am 2015; 62(4):857–871. doi: 10.1016/j.pcl.2015.04.002
17. Mehta RL. Glycemic control and critical illness: Is the kidney involved? J Am Soc Nephrol 2007; 18(10):2623–2627. doi: 10.1681/ASN.2007010109
18. Myers SR, Glaser NS, Trainor JL, Nigrovic LE, Garro A, Tzimenatos L, Quayle KS, Kwok MY, Rewers A, Stoner MJ, Schunk JE, McManemy JK, Brown KM, DePiero AD, Olsen CS, Casper TC, Ghetti S, Kuppermann N. Frequency and Risk Factors of Acute Kidney Injury During Diabetic Ketoacidosis in Children and Association With Neurocognitive Outcomes. JAMA Netw Open 2020; 3(12):e2025481. doi: 10.1001/jamanetworkopen.2020.25481
19. Orban JC, Maizière EM, GhaddabA, Van ObberghenE, IchaiC. Incidence and characteristics of acute kidney injury in severe diabetic ketoacidosis. PloS One 2014; 9(10):e110925. doi: 10.1371/journal.pone.0110925
20. Razavi Z. Frequency of Ketoacidosis in Newly Diagnosed Type 1 Diabetic Children Oman Med J 2010; 25(2):114–117. doi: 10.5001/omj.2010.31
21. Realsen J, Goettle H, Chase HP. Morbidity and mortality of diabetic ketoacidosis with and without insulin pump care. Diabetes Technol Ther 2012; 14(12):1149–1154. doi: 10.1089/dia.2012.0161
22. Rocktaeschel J, Morimatsu H, Uchino S, Goldsmith D, Poustie S, Story D, Gutteridge G, Bellomo R. Acid-base status of critically ill patients with acute renal failure: Analysis based on Stewart-Figge methodology. Crit Care Lond Engl 2003; 7(4):R60. doi: 10.1186/cc2333
23. Sutherland SM, Byrnes JJ, Kothari M, Longhurst CA, Dutta S, Garcia P, Goldstein SL. AKI in hospitalized children: Comparing the pRIFLE, AKIN and KDIGO definitions. Clin J Am Soc Nephrol 2015; 10(4):554–561. doi: 10.2215/CJN.01900214
24. Uber AM, Sutherland SM. Acute kidney injury in hospitalized children: Consequences and outcomes. Pediatr Nephrol Berl Ger 2020; 35(2):213–220. doi: 10.1007/s00467-018-4128-7
25. Uchino S, Bellomo R, Bagshaw SM, Goldsmith D. Transient azotaemia is associated with a high risk of death in

hospitalized patients. Nephrol Dial Transplant off Publ Eur Dial Transpl Assoc - Eur Ren Assoc 2010; 25(6):1833–1839. doi: 10.1093/ndt/gfp624

26. Vallon V, Thomson SC. Renal function in diabetic disease models: The tubular system in the pathophysiology of the diabetic kidney. Annu Rev Physiol 2012; 74:351–375. doi: 10.1146/annurev-physiol-020911-153333
27. Verny C. Congestive heart failure in the elderly diabetic. Diabetes Metab 2007; 33(1):S32-39. doi: 10.1016/s1262-3636(07)80055-3
28. Von Bibra H, St John Sutton M. Diastolic dysfunction in diabetes and the metabolic syndrome: Promising potential for diagnosis and prognosis. Diabetologia 2010; 53(6):1033–1045. doi: 10.1007/s00125-010-1682-3
29. Wagner A, RisseA, Brill HL, Wienhausen-Wilke V, Rottmann M, SondernK, Angelkort B. Therapy of severe diabetic ketoacidosis. Zero-mortality under very-low-dose insulin application. Diabetes Carevol 1999; 22(5):674–677. doi: 10.2337/diacare.22.5.674
30. Yang EM, Lee HG, Oh KY, Kim CJ. Acute Kidney Injury in Pediatric Diabetic Ketoacidosis. Indian J Pediatr 2021; 88(6):568–573. doi: 10.1007/s12098-020-03549-9
31. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs. chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA 2012; 308(15):1566–1572. doi: 10.1001/jama.13356
32. Zappitelli M, Parikh CR, Akcan-Arikan A, Washburn KK, Moffett BS, Goldstein SL. Ascertainment and Epidemiology of Acute Kidney Injury Varies with Definition Interpretation. Clin J Am Soc Nephrol 2008; 3(4):948–954. doi: 10.2215/CJN.05431207
33. Zhang Z, Xu X, Fan H, Li D, Deng H. Higher serum chloride concentrations are associated with acute kidney injury in unselected critically ill patients. BMC Nephrol 2013; 14:235. doi: 10.1186/1471-2369-14-235
34. Zubair M, Gad Mohamed N, Al Amri M, Begum S, Al-Balawy A, Sokair R, Ajwa I, Ajwa Clinical I. Clinical, demographic and biochemical profile of pediatric diabetic ketoacidosis patients in King Khalid Civilian Hospital, Tabuk. Medical Science 2018; 22(89),70-77