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Risk factors of acute kidney injury in children with diabetic ketoacidosis

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Abstract

Background Acute kidney injury (AKI) in pediatric patients has been linked to unfavorable short-term and long-term health outcomes. Despite the significance of AKI awareness in children with diabetes mellitus type 1 (T1D), the incidence of AKI in children admitted with diabetic ketoacidosis (DKA) has been under looked.

Objectives The primary objective of this study was to investigate the incidence of acute kidney injury (AKI) in pediatric patients hospitalized for diabetic ketoacidosis (DKA), and to identify the clinical and biochemical markers associated with the development of AKI.

Methods A retrospective medical record review was conducted at King Abdulaziz University Hospital, a tertiary hospital in Jeddah, Saudi Arabia. The study included 373 children aged 18 years or younger from 2012 to 2022 with complete medical records available for analysis. We collected baseline and diabetes characteristics, in addition to clinical variables at presentation. Acute kidney injury (AKI) was diagnosed using the serum creatinine criteria established by the kidney disease: Improving Global Outcomes (KDIGO) organization. Descriptive comparisons were performed. Uni- and multivariable logistic regression analyses were employed to identify potential risk factors associated with the development of AKI.

Results 299 patients (80.2%) developed AKI including 98 (26.3%) stage 1, and 118 (31.6%) stage 2 and 83 (22.3%) stage 3. The frequency of AKI was higher in patients with severe DKA (26.9% vs. 19.7%, p=0.01) while in mild DKA the percentage of AKI was less than non-AKI (31.9% vs. 45.1%, p<0.01The median last HbA1C prior to DKA presentation was 12%, and majority (88.2%) had DKA episodes in past. children who developed AKI had a significantly higher median heart rate (120 bpm, IQR 104–138) compared to those without AKI (108 bpm, IQR 98–124, p<0.01). A high percentage of children with AKI had low Glasgow coma scale (<15) compared to non-AKI (5.7% vs. 1.7%) but the difference was not statistically significant (p=0.22). Half of the children presented with DKA had poor outpatient follow up visits. The proven infections were observed in 53 (14.2%) children in DKA. It was higher in non-AKI group compared to AKI group (15.1% vs. 10.8%, p=0.46). At the time of discharge 131 (44%) patients with AKI showed persistent acute kidney disease. We did not observe mortality. Children with AKI had longer hospital stay compared to non-AKI (4 days vs. 3 days, p=0.02). None of the study participant have died during the studied hospital encounters.

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Conclusion Our findings indicate that AKI is common in children admitted with DKA. Longer duration and poor controlled T1D; previous episodes of DKA, severe DKA, infection and higher heart rate are risk factors to develop AKI. At the time of discharge, 131 (44%) patients AKI showed persistent acute kidney disease (AKD). The longer hospital stay in children with AKI highlights the significant morbidity of AKI.

Clinical trial number Not applicable.

Keywords Type 1 diabetes, Diabetes ketoacidosis, Pediatric, Acute kidney injury, Incidence rate

Background

Diabetic ketoacidosis (DKA) is a critical and potentially life-threatening complication of diabetes, particularly in children with type 1 diabetes (T1D). DKA is characterized by hyperglycaemia>250 mg/dl, metabolic acidosis with pH<7.3 and serum bicarbonate<15 mEq/l, and positive urinary ketone bodies [1].

DKA may present as an initial manifestation of T1D or occur in children with established T1D at any time during follow up particularly during episodes of intercurrent illness or insulin non-compliance [2].

The severity of DKA often necessitates hospitalization, as it poses significant risks of high morbidity and mortality due to cerebral edema [3]. To mitigate or prevent these complications an evidence-based protocol of timely assessment of fluid, electrolytes and hyperglycaemia management strategies has been recommended [4].

Acute Kidney Injury (AKI) is an important and common complication in children admitted with DKA and the incidence ranges from 14 to 47% [5, 6].

The most prevalent form of AKI in this demographic is functional AKI, primarily due to hypovolemia and impaired renal perfusion [7]. If severe or prolonged, this functional insult can lead to structural damage of the renal parenchyma and manifest as acute tubular necrosis (ATN). The incidence of severe AKI in children with DKA ranges from 21 to 35%. However, only 4% of patients who developed AKI received renal replacement therapy [6].

Despite the known risk of significant intravascular volume depletion in DKA and the implementation of cautious fluid management strategies, systematic studies on the incidence and impact of AKI in paediatric DKA patients remain limited. The multiple studies have highlighted the incidence of AKI in children with DKA ranging from 14 to 78%, emphasizing the potential for serious renal complications [6–10]. Currently, there is a strong evidence linking paediatric AKI to increased morbidity, mortality, and long-term risks of chronic kidney disease (CKD), therefore, understanding its prevalence and predictors of AKI in the context of DKA is crucial [11].

The primary objective of this study was to quantify the incidence of AKI among children with T1D hospitalized for DKA. Secondary objectives were to determine the association between clinical and laboratory markers particularly duration of DM, diabetic control, severity of DKA, and infection with the risk of AKI.

Methods

Study design and setting

This retrospective study was conducted at King Abdulaziz University Hospital (KAUH) in Jeddah, Saudi Arabia on children admitted with DKA from January 2012 to December 2022.

Participants

Included patients were 18 years of age or younger and had confirmed DKA, defined by a blood glucose level≥200 mg/dL, pH≤7.3 or bicarbonate level≤15 mEq/L, and elevated serum or urine ketones. Patients with incomplete medical record were excluded.

Ethical approval was taken from the KAUH Clinical Research Ethics Board. The patients' consent was not required due to the retrospective nature of the study.

Data collection

Data collection included comprehensive information on clinical history, physical findings, laboratory parameters including biochemical markers for estimated volume depletion and fluid resuscitation, presence of infection, severity of DKA and AKI, outcome as recovered, acute kidney disease were documented.

Study definitions

Acute kidney injury (AKI) was defined according to the Kidney Disease/Improving Global Outcomes (KDIGO) serum creatinine (*Cr*) criteria. KDIGO urine output criteria was not utilized due to inconsistent recording and osmotic diuretic effects on urine output. Due to the lack of pre-admission serum Cr values, we estimated the baseline Cr level (EBC) using an expected glomerular filtration rate (GFR) of 120 mL/min/1.73 m^2, based on the Schwartz equation. A GFR of 120-ml/min/1.73 m^2 was chosen based on established standards in pediatric AKI studies. Additionally, a GFR of 90 mL/min/1.73 m^2 was used in a sensitivity analysis for conservative estimates of AKI.

AKI stages: AKI was classified according to KDIGO criteria.

- Stage 1: Creatinine values≥1.5 but <2 times the estimated basal creatinine.
- Stage 2: Creatinine values≥2 but <3 times the EBC.
- Stage 3: Creatinine values≥3 times the EBC.

Patients with AKI and had high serum creatinine persisting for >7 but less than 3 months were classified as acute kidney disease (AKD), whereas patients with high serum creatinine persisting for more than 3 months were classified as CKD.

Severity of metabolic acidosis: The severity of DKA was documented at presentation as the following.

- Mild: venous pH>7.2 and <7.3, bicarbonate<15 mmol/l,
- Moderate: venous pH>7.1 and <7.2, bicarbonate<10 mmol/l and.
- Severe: venous pH<7.1, bicarbonate<5 mmol/l.

Infections/sepsis: Infectious episodes were documented in all cases and evaluated for association of risk of AKI.

Data analysis

Descriptive statistics were used to summarize baseline demographics, characteristics of DM, DKA and AKI parameters. Continuous variables were assessed for normality using the Shapiro–Wilk test. Normally distributed variables were presented as means with standard deviations and compared using Student's t-test, while non-normally distributed variables were presented as medians with interquartile ranges and compared using the Mann–Whitney U test. Categorical variables were presented as percentages and compared using chi-squared or Fisher's exact tests, as appropriate. Univariate logistic regression analyses were performed to identify factors associated with AKI development, using AKI as the dependent variable and demographic, baseline diabetes, and DKA characteristics as independent variables. Significant predictors from univariate analyses were included in a multivariate logistic regression model. The results were expressed as odds ratios with 95% confidence intervals, and the area under the receiver operating characteristic curve (AUC) was calculated for the combined model predicting AKI. Statistical significance was set at $p<0.05$. Data were collected using Microsoft Excel® and analyzed with Stata version 18 (Stata Corp, TX, USA).

Results

We included 373 children who presented with diabetic ketoacidosis (DKA) at King Abdulaziz University Hospital, with a median age of 132 months (IQR 96–156) (Table 1).

AKI was observed in 299 children (80.2%), categorized as Stage 1 in 98 (26.3%), Stage 2 in 118 (31.6%), and Stage 3 in 83 (22.3%) (Table 2).

Table 3 shows the DM characteristics of patients presented with DKA. Diabetes mellitus (DM) was diagnosed at a median age of 108 months (IQR 60–132). The interval between diabetes diagnosis and DKA presentation was significantly longer in children who developed AKI (median 72 months, IQR 48–108) compared to those without AKI (median 60 months, IQR 24–96, $p=0.01$) (Table 3). The median HbA1c level before DKA presentation was 12% (IQR 9.9–13.8), and most children (88.2%) had previously experienced DKA episodes (Table 3). Notably, half of the children did not have documented outpatient follow-up visits. Conventional insulin therapies were used in 77.8% of cases (Table 3). Conversely, uncontrolled diabetes (HbA1c>8%) was more prevalent in the AKI group (92.3% vs. 79.7%, $P=0, 01$) (Table 3).

Table 2 shows the clinical, laboratory characteristics, severity and outcome of AKI patients in the study population. The severity of DKA was classified as mild in 127 (34%), moderate in 126 (33.7%), and severe in 94 (25.2%) patients, respectively. Among the DKA characteristics, the incidence of AKI was higher in children with severe DKA (26.9% vs. 19.7%, $p=0.01$) and lower in those with mild DKA (31.9% vs. 45.1%, $p<0.01$) (Table 3). The hospital length of stay was longer for children with AKI, with a median of 4 days (IQR 2–6) compared to 3 days (IQR 2–5) for those without AKI ($p=0.07$) (Table 2).

At presentation, children who developed AKI had a significantly higher median heart rate (120 bpm, IQR 104–138) compared to those without AKI (108 bpm, IQR

Table 1 Demographic of patients with diabetic ketoacidosis (DKA)

	Children with DKA			*p*-value
	Total	No AKI	AKI	
Number (%)	373	74 (19.8%)	299 (80.2%)	
Demographics at presentation				
***Age**, months (median [IQR])*	132 (96–162)	132 (84–156)	132 (108–168)	0.32
***Sex**, male (n [%])*	140 (37.5%)	25 (33.8%)	115 (38.5%)	0.50
***Weight**, kg (median [IQR])*	30 (20-43.4)	30 (20–40)	30 (20–45)	0.58
***Height**, cm (median [IQR])*	139 (117–150)	137 (120–150)	140 (116.5–150)	0.70
***Body mass index**, kg/m^2(median [IQR])*	17.4 (14-21.1)	17.6 (14-20.8)	17.2 (13.9–21.3)	0.91
***Nationality**, Saudi (n [%])*	178 (47.9%)	40 (54.1%)	138 (46.3%)	0.24

Table 2 Severity and outcome of AKI in patients with diabetic ketoacidosis

	Children with DKA			*p*-value
	Total	**No AKI**	**AKI**	
Number (%)	373	74 (19.8%)	299 (80.2%)	
Hospital location				
Emergency, *(n [%])*	5 (1.4%)	1 (1.4%)	4 (1.3%)	1.00
Ward, *(n [%])*	293 (79.0%)	57 (79.2%)	236 (78.9%)	
ICU, *(n [%])*	73 (19.7%)	14 (19.4%)	59 (19.7%)	
ICU length of stay, *days (median [IQR])*	2 (1–3)	2 (1–2)	2 (1–3)	0.45
Vital signs at admission				
Systolic BP, *mmHg (median [IQR])*	112 (105–122)	112 (105–120)	112 (105–123)	0.55
Diastolic BP, *mmHg (median [IQR])*	69.5 (62–77)	68 (61–74)	70 (62–77)	0.12
Heart rate, *bpm (median [IQR])*	117 (102–134)	108 (98–124)	120 (104–137)	**< 0.01**
Temperature, *℃ (median [IQR])*	36.9 (36.6–37.1)	36.9 (36.5–37.1)	36.9 (36.6–37.1)	0.67
Presence of infection, *(n [%])*	53 (14.2%)	8 (10.8%)	45 (15.1%)	0.46
Glasgow Coma Scale				
15, *(n [%])*	355 (95.2%)	73 (98.7%)	282 (94.3%)	0.22
< 15, *(n [%])*	18 (4.8%)	1 (1.4%)	17 (5.7%)	
Severity of DKA				
Unknown, *(n [%])*	25(6.0%)	11 (3%)	14 (3.7%)	**0.01**
Mild, *(n [%])*	127 (34%)	32 (45.1%)	95 (31.9%)	
Moderate, *(n [%])*	126 (33.7%)	17 (23.9%)	109 (36.6%)	
Severe, *(n [%])*	94 (25.2%)	14 (19.7%)	80 (26.9%)	
Baseline laboratories				
HbA1C, *% (median [IQR])*	12.9 (10.9–14.1)	12.3 (10.5–14.2)	13 (10.9–14.1)	0.51
Bicarbonate, *mEq/L (median [IQR])*	10 (6–12)	10.5 (5.5–13)	9 (6–12)	0.24
Na correction, *mEq/L (median [IQR])*	140 (136–145)	140 (137–144)	140 (136–145)	0.63
Hospital length of stay, days (median [IQR])	4 (2–6)	3 (2–5)	4 (2–6)	0.07
AKI stage				
Stage 1, *(n [%])*	-	-	98 (26.3%)	-
Stage 2, *(n [%])*			118 (31.6%)	
Stage 3, *(n [%])*			83 (22.3%)	
Patients with AKD at time if discharge AKD, *([%])*	131 (35.1%)	0	131 (44.0%)	**< 0.01**
CKD				
Mortality	0 (0)	0 (0)	0 (0)	-

98–124, $p<0.01$) (Table 2). Although a higher proportion of AKI patients had a Glasgow Coma Scale (GCS) score of less than 15 (5.7% vs. 1.7%), this difference was not statistically significant ($p=0.22$) (Table 2). There was 53 (14.2%) children with proven infections; 8(10.8%) in non-AKI group and 45 (15.1%) in AKI group ($p=0.46$).

However, there was no mortality but a significant number of patients had AKD (44%). None of the study participant have died during the studied hospital encounters.

Univariable logistic regression analyses showed significant associations between AKI and the duration of DM prior to DKA, diabetes control (HbA1c≤8 vs. >8), DKA severity, and heart rate at presentation (Table 4). In the adjusted multivariable logistic regression model for age, gender and infections, heart rate, diabetes duration, and glycemic control remained significantly associated with AKI, with an area under the receiver operating characteristic curve (AUC) of 0.68 (95% CI: 0.61–0.75, $p<0.01$) (Table 4).

Discussion

Our study revealed that a substantial proportion (80.2%) of children with DKA developed AKI. Huang et al. reported 56.5% of AKI among 223 participants with 301 episodes of DKA. Notably, one-third of children with AKI had severe AKI, indicating not only volume-responsive renal injury yet also intrinsic renal tubular injury [12]. Hursh et al. evaluated 165 children hospitalized for DKA and found a 64.3% prevalence of AKI; the AKI definition used in this study was based on the KDIGO criteria [7]. However, this incidence is notably higher compared to the 40% reported by Bergmann, highlighting variability in AKI prevalence across different studies [13]. The magnitude of AKI in our study (80.2%) is higher than all three above quoted studies [7, 12, 13]. This discrepancy may be attributed to differences in definitions and diagnostic criteria for AKI, emphasizing the need for standardized criteria in paediatric populations.

Table 3 DM characteristics of patients with diabetic ketoacidosis (DKA)

	Children with DKA			*p*-value
	Total	No AKI	AKI	
Number (%)	373	74 (19.8%)	299 (80.2%)	
Baseline diabetes characteristics				
Age of onset, *months (median [IQR])*	108 (60–132)	108 (72–132)	108 (60–132)	0.41
Duration of DM, *months (median [IQR])*	72 (48–108)	60 (24–96)	72 (48–108)	**0.01**
Last HbA1C, *% (median [IQR])*	12.1 (9.9–13.8)	11.6 (9-13.8)	12.2 (10-13.8)	0.16
History of previous DKA, *(n [%])*	329 (88.2%)	67 (90.5%)	262 (87.9%)	0.69
Number of outpatient visits				
No visits, *(n [%])*	190 (50.9%)	40 (54.1%)	150 (50.2%)	0.78
1–2 visits, *(n [%])*	86 (23.1%)	17 (23.0%)	69 (23.1%)	
≥ 3 visits, *(n [%])*	97 (26%)	17 (23.0%)	80 (26.8%)	
Insulin regimen type				
Conventional therapy, *(n [%])*	287 (77.8%)	58 (79.5%)	229 (77.4%)	0.76
MDI therapy, *(n [%])*	82 (22.2%)	15 (20.6%)	67 (22.6%)	
Diabetes control				
Controlled (HbA1C < = 8), *(n [%])*	38 (10.2%)	15 (20.3%)	23 (7.7%)	**< 0.01**
Uncontrolled (HbA1C > 8), *(n [%])*	335 (89.8%)	59 (79.7%)	276 (92.3%)	

MDI: Multiple Daily Injection

Table 4 Multivariable logistic regression analysis for predictor variables associated with AKI development in children with DKA

Variable	Multivariable logistic regression				Adjusted multivariable logistic regression*			
	OR	95% CI		*p*-value	OR	95% CI		*p*-value
Duration of DM	**1.01**	**1.00**	**1.01**	**0.049**	1.01	1.00	1.01	0.056
Uncontrolled DM (> 8)[€]	**3.81**	**1.69**	**8.57**	**0.001**	**3.59**	**1.56**	**8.26**	**0.003**
Heart rate	**1.01**	**1.00**	**1.02**	**0.017**	**1.01**	**1.00**	**1.03**	**0.015**
Severity of DKA^								
Mild	1.48	0.53	4.18	0.454	1.63	0.57	4.67	0.366
Moderate	**3.69**	**1.27**	**10.70**	**0.016**	**4.09**	**1.38**	**12.11**	**0.011**
Severe	**2.79**	**0.94**	**8.29**	**0.065**	**3.16**	**1.03**	**9.65**	**0.043**

* Adjusted for age of presentation, sex, and the presence of infection

[€] Reference: controlled DM (HbA1C < = 8)

^ Reference: unknown DKA severity

The prevalent stages of AKI severity (stage II+III) was 41.77% reported by Al-Khalifa et al. [14]. In comparison, the prevalence in our cohort of combined severity of AKI (stage II+III) was 53.9%.

The high incidence of severe AKI observed in our cohort suggests that a significant number of children with DKA experience intrinsic renal damage rather than just functional AKI or volume-responsive AKI. This finding underscores the severity of renal complications in DKA and indicates that a substantial portion of DKA cases can lead to significant renal impairment. A recent systemic review shows pooled prevalence of severe AKI in 28% among patients with overall prevalence of AKI was 47% [6].

Our study identified several clinical and biochemical factors associated with AKI development including duration of T1D, glycaemic control. This study showed that prolonged duration of uncontrolled T1D more than 8 years linked to the development of AKI.

We showed that elevated HbA1C linked to AKI in children with DKA This aligns with findings from a large New Zealand study, which showed higher HbA1C in children with AKI compared to non -AKI (p-value 0.04) [15]. These results highlight the critical role of effective diabetes management by regular follow up and maintaining good control of HbA1C to decrease AKI episodes in vulnerable population.

Interestingly, while some studies have identified high sodium levels (≥145 mEq/L), at admission as predictors of more severe AKI [16], we did not find a significant difference in serum sodium levels between patients with and without AKI (P=0.88). This discrepancy may be due to variations in patient populations, measurement techniques, or other confounding factors.

Our study did demonstrate that a higher heart rate at admission was associated with an increased likelihood of developing AKI. This finding supports the hypothesis that severe volume depletion, as reflected by elevated heart rates, plays a crucial role in AKI development in

children with DKA [12, 17]. However, it is important to note that overzealous fluid resuscitation can lead to hyperchloremia, which has been associated with prolonged recovery time from AKI [18]. Thus, balanced fluid management remains essential to avoid exacerbating renal injury while treating DKA.

Our findings suggest that the severity of the DKA episode correlates with the likelihood of AKI development (Table 4), consistent with other studies indicating that severe metabolic derangements. Huang showed that patients with AKI tends to have more severe acidosis (pH 7.15) compared to non-AKI (pH of 7.20, p-value 0.01) [12].

While some studies have shown that initial high-volume intravenous boluses do not significantly differ in AKI resolution compared to low-volume boluses [18], it is important to keep careful fluid management tailored to individual patient needs.

Infection is a significant triggering factor for developing DKA [19, 20] and may be a major contributing cause for AKI. In our study, the incidence of infection rate was higher among patients with AKI compared to non-AKI, although the difference was not statistically significant. However early diagnosis and management of infection in DKA patients remains crucial and may help improve the outcomes of DKA and AKI.

Furthermore, a low Glasgow Coma Scale (GCS) score (less than 15) was prevalent (5%) among children with AKI compared to non-AKI in our study. Previous research has suggested that a GCS score of less than 14 is a risk factor for moderate to severe AKI, highlighting the importance of monitoring neurological status in these patients [21].

Our study showed that number of patients with renal impairment at time of discharge was significantly high in patients who developed AKI indicating that a significant intrinsic renal damage can occur in patients with DKA and AKI.

More studies are needed to assess long- term outcome for renal function.

Study limitations and future directions

The primary limitation of this study is its retrospective design, which inherently relies on the accuracy and completeness of medical records. The retrospective nature may affect the precision of the data and limit the ability to establish causality. Future prospective studies with well-defined comparator populations and standardized diagnostic criteria are needed to validate these findings and further elucidate the risk factors for AKI in paediatric DKA patients.

Conclusion

This study provides substantial evidence of the high incidence of AKI among patients hospitalized with DKA at a local setting.

Our findings indicate a strong association between incidence of AKI and severity of DKA. Patients with longer duration of T1D and poor glycaemic control were associated with higher incidence of AKI. A high percentage of patients with DKA developed AKI had persistent AKD indicating significant intrinsic renal damage. While in our study there was no mortality and none of our patients needed dialysis, AKI still pose significant morbidity and mortality with AKI highlight the urgent need for effective strategies to prevent, diagnose, and manage AKI in children with T1D and DKA.

Abbreviations

AKI	Acute Kidney Injury
AKD	Acute Kidney disease
DKA	Diabetic Ketoacidosis
T1D	Type 1 Diabetes
KAUH	King Abdulaziz University Hospital
KDIGO	Kidney Disease Improving Global Outcomes
AUC	Area Under Curve
GCS	Glasgow Coma Scale

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Author contributions

DA, AA, collected the data. IS performed statistical analysis. MS, MA, SB, MS reviewed the results NY, OS, JK a senior authors who revised the manuscript. All authors Wrote the manuscript and discussed the results.

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Data availability

The dataset used and /or analyzed during the current study are valuable upon the request from the corresponding author.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and with the Ethical Guidelines for King Abdulaziz University. The study was approved by the Ethics Review Committee of King Abdulaziz University Hospital. Letter no 14567 issued on January 2024. As the data were collected retrospectively from patient charts, informed consent was deemed unnecessary following the national guidelines and IRB Committee of King Abdulaziz University.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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