Kufa Medical Journal | Vol. 20, No. 2, 2024

Original article | DOI: https://doi.org/10.36330/kmj.v20i2.16576

p-ISSN: 1993-517X

e-ISSN: 2709-4464

Acute Kidney Injury in Children with Diabetic Ketoacidosis

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ABSTRACT

Backgrounds and Objectives: *Diabetic ketoacidosis is frequent in type I diabetic children, and as acute kidney injury has a well-known morbidity, this study aims to determine the frequency and associated factors of acute kidney injury in these children.* ***Material and Methods****: A prospective study conducted on type I diabetic children with diabetic ketoacidosis admitted at Central Child Teaching Hospital; during February 2020 - January 2021. The study includes 96 patients, aged < 15 years. Demographic and clinical information collected for each patient, including (age, gender, onset of diabetes, previous diabetic ketoacidosis, recurrent urinary tract infection). At admission all patients underwent clinical assessment of their heart rate and amount of resuscitation boluses given; and weight and height measured. PH and HCO3 levels used to categorize diabetic ketoacidosis severity. Kidney Disease Improving Global Outcomes S.creatinine criteria used to identify acute kidney injury. Estimated basal creatinine using modified Schwartz formula, with glomerular filtration rate 120 ml/min/m2 was used. Logistic regression analysis used to identify risk factors.* ***Results:*** *A total 19 (19.8%) participants developed acute kidney injury(AKI) at 24hrs hospitalization [15 (78.9%) cases AKI stage I, 2 (10.5%)cases AKI stage II, and 2 (10.5%)cases AKI stage III]. One child required peritoneal dialysis at second day of admission. Diabetic ketoacidosis severity odds for AKI reached 5.5 and increased to 13.3 with increasing heart rate.* ***Conclusions:*** *Acute kidney injury occurred in one in five of children during diabetic ketoacidosis with ketoacidosis severity and high heart rate at admission is an important associated factors.*

Keywords: Acute Kidney Injury, Diabetic Ketoacidosis, Type I Diabetes.

Article Information

Received: June 14, 2024; Revised: August 30, 2024; Online December, 2024

INTRODUCTION

Ketoacidosis is responsible for the initial presentation of many (about 25%– 40%) diabetic children. In children with established type 1 diabetes mellitus ,the condition is a metabolic derangement caused by the absolute or relative deficiency of insulin , together with the major complication of cerebral edema , it is the most important cause of mortality and severe morbidity in children of diabetes .The risk of diabetic ketoacidosis(DKA) is (1-10)% per patient per year.(1) In diabetic patients kidney injury is a major complication and while acute kidney injury(AKI) is previously recognized as uncommon complication associated with DKA,(1) Since a time going back to 1993, cases reported diabetic patients who developed AKI while admitted with DKA. In recent years, research papers from different regions in the

world started to turn out that AKI in DKA is frequent and real concern with an associated long term renal complication.(2-4) Diabetes is the principal cause for patients requiring renal replacement therapy worldwide.(5) AKI is associated with adverse outcomes both in the short and long term with chronic kidney disease being increasingly recognized as a common sequela of AKI(6). In March 2012, Kidney Disease Improving Global Outcome (KIDGO) define the diagnoses of AKI by an absolute increase in serum creatinine, at least 0.3 mg / dl (26.5 mmol/ L) within 48 hours or by a 50% increase in serum creatinine from baseline within 7 days, or a urine volume of less than 0.5 ml / kg / hr for at least 6 hours .(7) Estimating creatinine baseline pre-illness is best achieved when a previously drawn serum creatinine level is available. If not, the baseline kidney function in children can be estimated using the Schwartz formula.(8,9) *Schwartz formula:* *Glomerular filtration rate (GFR)* (ml/min/1.73 m2) = K × Ht ÷ Pcr. Ht = height in cm, and Pcr = plasma creatinine, K= (61.9 in males 13 years and older, 39.8 in infants, and 48.6 in all other children).(8-10)

Creatinine measurement methods and ketoacids: Manufacturers have developed two families of creatinine assays: Jaffe creatinine methods and enzymatic methods that appear specific for creatinine.(11) Both are colorimetric methods. In Jaffe methods, reaction to serum creatinine is not fully specific that acetoacetate cause severe interference, which might influence therapeutic decisions at the start of diabetic ketoacidosis. Meanwhile, Enzymatic assays are more specific and lack this interference. (12,13) Enzymatic creatinine values tend to run lower than those determined by the Jaffe method, especially at low level of serum creatinine resulting in overestimation of GFR if used with "k" values used in Schwartz formula. Thus, the Schwartz formula for eGFR was revised to overcome the approximately 20-30% bias of GFR overestimation. This "modified Schwartz formula" used a single value of k = 0.413 for all age groups. *Modified Schwartz formula:* eGFR = 0.413 x height (cm) / Pcr (mg/dl).(10,12,14.)

METHOD

Data Source

A prospective observational study conducted at the emergency department of Child Central Teaching Hospital (a tertiary pediatric hospital) in Baghdad, Iraq; during the period from February 8, 2020 till January 28,2021. Included were children with type I diabetes, known cases or new cases (all have a classical Type 1 diabetes presentation of: Short history of polyuria, polydipsia with glucosuria, ketonuria, and random blood glucose of ≥ 200 mg/dl (11.1 mmol/L)). New cases diagnosed using the criteria of HgA1c > 6.5%.(15) Patients were (1-15) year old and admitted with diabetic ketoacidosis(DKA) and completed 24 hrs of hospitalization. A total of 96 cases selected according to the inclusion criteria. Cases with signs and symptoms of Type 2 diabetes (obesity and acanthosis nigricans) or had chronic illness other than diabetes where excluded. During data collection, 3 cases admitted twice with DKA episode and one case for 3 times. Recurrent admissions of same patient were dealt with as an isolated event.

Data collection and case definition

Demographic and clinical history collected from each patient and his/her caregiver during admission (age and gender; history of diabetes onset and duration, previous DKA episodes, history of recurrent urinary tract infection (UTI), and history of previous renal disease or other chronic illness). Clinical assessment was done at time of admission of heart rate and amount of resuscitation fluid boluses given. Age categorized into 3 groups toddlers <5, child 5-12, teenage>12.(16) The Heart rate categorized relative to its increase from upper limits of normal for age and gender.(17) Anthropometric measurements of weight in kilograms (Kg) and

height in centimeters (cm) measured during current admission either at admission or after early stabilization using height measuring stand - stadiometer with weighing scale (Asimed medical apparatus Mod: MB201T PLUS, Max: 150 kg, Min: 2000g). Body mass index (BMI) calculated using the following equation (BMI = weight (in Kg) / height (in M)2), and results plotted and categorized according to CDC percentiles for age and gender.(18) DKA severity (as recommended in the 2020 BSPED DKA protocol) was classified as Mild(pH 7.2-7.29 &/or bicarbonate < 15 mmol/l), moderate(pH less than 7.1-7.19 &/or bicarbonate < 10 mmol/l), severe(pH less than 7.1 &/or bicarbonate < 5 mmol/l).(19,20) Patients who fulfill KDIGO definition of AKI were staged according to serum creatinine into mild, moderate, and severe AKI.(7,21) Modified Schwartz formula: e GFR = 0.413 x height (cm) / P cr (mg/dl) was used.(14) None of included patients had previous basal creatinine, eGFR of 120 ml/min/1.73m2 was used as it was standardized in previous study designs.(9,10) We hadn't applied the KDIGO urinary output criteria for AKI as many patients in the study had no reliable way to collect and measure their urinary output. For each patient, results of two blood samples collected, one immediately after admission and the other after 24 hrs. of management. Serum creatinine measured by (DiaSys respons 920) which uses enzymatic method in measuring creatinine, and HCO3 and PH with blood gas analysis using radiometer (ABL 827 Flex Plus). Association of DKA acidosis and dehydration (at admission) to AKI occurrence (after 24hrs) hospitalization were sought. In the hospital all patients included were managed according to 2020 BSPED DKA management guidelines **(19).**

Statistical analysis

The data analyzed using Statistical Package for Social Sciences (SPSS) version 25. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Chi square test was used to assess the association between frequency of AKI after 24 hours and parameters at admission, while fisher exact test was used instead when the expected frequency was less than 5. Logistic regression analysis with RStudio was applied using AKI after 24 hours as the dependent variable and the OR and 95% CI of selected independent variables shown. A level of P – value less than 0.05 was considered significant.

RESULTS

Study cases mean age 9.73 years with (2-15) years range, and male to female ratio 1:1.46. In study, 54(56.3%) were known case of diabetes. At admission, 24(25%) of study patients developed AKI and after 24 hrs 14(14.6%) continue to had AKI and 5(5.2%) patients whom was normal at admission developed AKI after 24hrs. One patient had severe AKI and needed renal replacement therapy with peritoneal dialysis for two days started 24 hrs after management with DKA protocol.

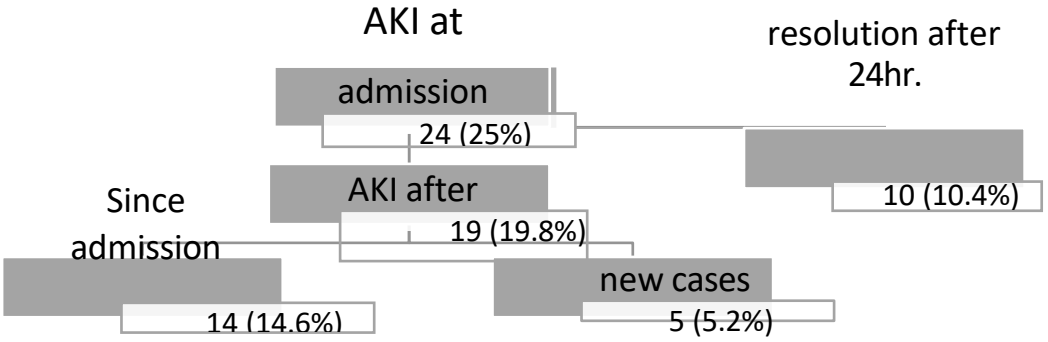

Figure 1: Frequency of AKI at Admission and 24hrs later.

Table 1: The association of AKI after 24 hrs with demographic and clinical history of patients.

Variable	AKI after 24 hrs.		Total (%) n= 96	P – Value
	Yes (%) n= 19	No (%) n= 77		
Age Group (Years)				
< 5	2 (15.4)	11 (84.6)	13 (13.5)	0.239
5 – 12	8 (15.1)	45 (84.9)	53 (55.2)	
> 12	9 (30.0)	21 (70.0)	30 (31.3)	
Gender				
Male	5 (12.8)	34 (87.2)	39 (40.6)	0.156
Female	14 (24.6)	43 (75.4)	57 (59.4)	
BMI centile for age				
< 5th	5 (16.1)	26 (83.9)	31 (32.3)	0.618
5th – 50th	7 (17.1)	34 (82.9)	41 (42.7)	
51th – 75th	2 (28.6)	5 (71.4)	7 (7.3)	
76th – 95th	5 (29.4)	12 (70.6)	17 (17.7)	
Diabetes Mellitus				
Known case	11 (20.4)	43 (79.6)	54 (56.3)	0.871
Newly diagnosed	8 (19.0)	34 (81.0)	42 (43.8)	
Heart rate for age				
Tachycardia	18 (23.1)	60 (76.9)	78 (81.3)	0.092
Normal	1 (5.6)	17 (94.4)	18 (18.7)	
Fluid bolus given (ml/kg)				
10	7 (12.5)	49 (87.5)	56 (58.3)	0.068
20	7 (25.9)	20 (74.1)	27 (28.1)	
> 20	5 (38.5)	8 (61.5)	13 (13.5)	
DKA severity				
Mild	1 (1.8)	55 (98.2)	56 (58.3)	0.001
Moderate	9 (42.9)	12 (57.1)	21 (21.9)	
Severe	9 (47.4)	10 (52.6)	19 (19.8)	
Previous DKA				
No	11 (19.6)	45 (80.4)	56 (58.3)	0.943
1 – 5	5 (18.5)	22 (81.5)	27 (28.1)	
> 5	3 (23.1)	10 (76.9)	13 (13.5)	

Logistic regression analysis was applied using AKI after 24 hrs. as dependent variable and various demographic and clinical presenting factors as independent variable. Factors representing the severity of DKA and increasing HR above normal for age at presentation were found to be significantly independent risk factors for greater likelihood of AKI.

Table 2: Logistic regression analysis for association of DKA severity and increasing HR with frequency of AKI after 24 hrs.

Characteristics	AKI*	
	Adjusted OR	95% CI
Patients Demographic		
Age (years)	1.10	(0.87-1.45)
Past Clinical Condition		
Diabetes duration(years)	0.77	(0.58-1.18)
Recurrent UTI	0.23	(0.14-2.38)
Presenting Clinical Condition		
DKA severity		
Mild	*Ref.*	
Moderate	5.53 ***	(7.79-11.91)
Severe	3.18 **	(4.35-7.12)
Heart rate above normal (/min)	13.30 **	(4.85-11.42)

Significance codes: 0 '*' 0.001 '**' 0.01 '*' 0.05**

***Reference category: No AKI**

AKI, Acute Kidney Injury; OR, Odds Ratio; CI, Confidence Interval; UTI, Urinary Tract Infection; DKA, Diabetic Ketoacidosis. An estimated glomerular filtration rate of 120 ml/min/1.73m2 to define AKI.

DISCUSSION

In our study we included 96 type I diabetic children admitted with an episode of DKA, as shown in the (Fig.1) 19.8% of them developed AKI 24hrs after early stabilization with DKA protocol, one of them needed renal replacement therapy and five of them who hadn't have AKI at admission developed AKI after 24hrs of early stabilization and rehydration with DKA management protocol. Other studies found AKI frequency to be 28.3% as in the study of Yang et al, (22) with increasing incidence reaching to 64.2% in Hursh et al study, or even to 80.75% as what Al Khalifah et al show in their study.(23, 24) Our study support many studies that is raising concern on AKI being a frequent complication in children presented with DKA. In a systematic review on Twenty-one studies assessing 4087 children (4500 DKA episodes)

reported AKI during DKA episodes, Meena and Yadav, et al., found the AKI pooled incidence to be 47% which even exceed what we show in our results (25). The age, gender, BMI, and previous DKA episodes all showed no significant association to AKI. To our knowledge, no association was seen in previous studies as well, except Myer et al who found a higher association with older age and AKI prevalence but then down placed this result after adjusting for the study sensitivity(26).

Diabetes duration, categorized by 'patients diagnosed' or 'new cases', hasn't shown any association to AKI prevalence, and while Hursh et al and Baalaaji et al saw no association as well; (23,27) Yang et al, Myer et al, and Huang et al all found a significant increase of AKI in patients who previously diagnosed with DM compared to those with new onset diabetes.(22,26,28.) The design of studies and the prolonged period of data collection with time reaching up to 15 and 17 years may explain those studies ability to reveal such a very possible association. In a binominal logistic regression analysis we found that moderate to severe DKA and increasing heart rate to have a significant effect on AKI. While parameters that may point to previous condition of the kidney, like history of recurrent UTI and duration of diabetes show no statistically significant effect on AKI. Hursh et al who found that a lower serum bicarbonate level of less than 10 mEq/L (which includes moderate and severe DKA) associated with more than 10-fold increase in the odds of severe AKI.(23) Although other studies which hadn't categorized DKA severity, their results showed a significant association between low PH and/or Low HCO3 level and AKI development and severity.(25) Baalaaji et al founded the same significant association with HCO3 level at 24 hours but not at admission.(27) Myer et al and Huang et al, all showed that increasing heart rate at admission significantly associated with AKI(26,28).

CONCLUSIONS

This study showed that AKI had occurred in one in fifth in children with type 1 diabetes presented with DKA and severity of the acute presentation of DKA represented by acidosis severity and increasing heart rate (which may points to degree of acidosis) has a significant effect on AKI occurrence during DKA episode. The results are rising concern that AKI in DKA is a possible risk for intrinsic renal injury and studies on the long term effect of DKA episodes on kidney injury is important.

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