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BRIEF COMMUNICATIONS

Acute Kidney Injury in children with diabetic ketoacidosis at onset and diabetic kidney disease: a case-control study

Lesión Renal Aguda en niños que debutan con cetoacidosis diabética y enfermedad renal por diabetes: estudio de casos y controles

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What do we know about the subject matter of this study?

Acute kidney injury (AKI) increases the likelihood of chronic kidney disease. Although many children with type 1 diabetes (T1D) and diabetic ketoacidosis (DKA) develop AKI, there is little information on the association between this complication and renal outcome.

What does this study contribute to what is already known?

This case-control study revealed that the presence of AKI during DKA at the onset of T1D independently increased the likelihood of diabetic kidney disease (DKD) more than fivefold at 8 years of follow-up. Given that AKI was already present at the time of hospitalization, interventions to prevent DKA and, consequently, AKI could reduce the likelihood of DKD.

Abstract

During diabetic ketoacidosis (DKA), acute kidney injury (AKI) may occur. **Objective**: To evaluate the association between the presence and severity of AKI during the onset of DKA in patients with type 1 diabetes (T1D) and the development of diabetic kidney disease (DKD). **Patients and Method**: Case-control study. Patients with T1D who presented with DKA at onset and later developed DKD were identified from a local database. Controls were T1D patients with DKA at onset but without DKD. The presence of AKI at onset was assessed as a factor associated with DKD. Exclusion criteria included missing critical data in medical records, follow-up shorter than 8 years from the onset, kidney disease of a different etiology, and/or initial treatment at a different center. The outcome measure was renal status (presence or absence of DKD) at 8 years after T1D onset. **Results**: Seventeen cases and 42 controls were studied; 22 patients developed AKI. Cases had higher HbA1c levels from the onset ($p = 0.004$) and a higher frequency ($p = 0.001$) and severity ($p = 0.012$) of AKI during DKA. Only AKI (OR 5.4, 95% CI 1.18-24.6; $p = 0.02$) remained independently associated with DKD. **Conclusion**: AKI during the onset of DKA in T1D patients was associated with the development of DKD.

Keywords:
Diabetic Ketoacidosis; Acute Kidney Injury; Diabetic Kidney Disease; Diabetic Nephropathy; Type 1 Diabetes; Children

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Introduction

Diabetic kidney disease (DKD) increases morbidity in young people with type 1 diabetes (T1D)[1]. Both non-modifiable risk factors (sex, duration of T1D, and genetic predisposition) and modifiable risk factors (obesity, glycemic control, hyperlipidemia, and hypertension) are associated with the development of DKD[2]. Renal structural changes in DKD include thickening of the glomerular basement membrane, podocyte injury, and mesangial expansion, leading to tubulointerstitial fibrosis and glomerulosclerosis[3]. These changes manifest as glomerular hyperfiltration, albuminuria, proteinuria, and decreased glomerular filtration rate (GFR)[1]. In pediatrics, although advanced stages of DKD are uncommon, up to 20% of patients present with albuminuria after 5 years of disease progression[1].

In recent years, there has been growing recognition that episodes of acute kidney injury (AKI) of different etiologies increase the risk of chronic kidney disease (CKD)[4]. Although a high proportion of children hospitalized due to diabetic ketoacidosis (DKA) present with AKI[5,6], there is little information on the impact of this complication on subsequent renal outcomes[7]. The objective of this study was to evaluate whether the presence and severity of AKI during DKA at the onset of T1D are associated with the development of DKD.

Patients and Method

Case-control study, conducted in a tertiary pediatric hospital. The cases were patients with T1D with DKA at the onset and DKD identified in our database. Controls were patients with T1D and DKA at the onset, without DKD seen on the same day as the cases. The outcome measure was renal status at 8 years of T1D progression, and the exclusion criteria were absence of critical data in the medical records (creatinine value or creatinine during DKA, proteinuria, and/or albuminuria in the renal evaluation at 8 years of disease progression), follow-up of less than 8 years from the onset, kidney disease due to a different cause or before the diagnosis of T1D, and/or treatment at the onset in another center. We established renal status (presence or absence of DKD) at 8 years of T1D progression as the outcome measure because DKD is uncommon before 5 years of the onset[6], so we considered that this time interval would be sufficient to demonstrate potential renal damage related to AKI. In addition, given that diabetes usually develops between 3 and 8 years of age, and that DKD appears after 5 years of disease progression, we considered that this time window would also optimize patient inclusion, since from the age of 15, some of them begin the transition to adult care centers.

DKA was managed in all cases according to our hospital's protocol[8], which follows the ISPAD[9] guidelines in force at the disease onset in the patients included in this study. In our department, follow-up after diagnosis consists of quarterly visits that include a physical examination and monitoring of blood pressure and HbA1c levels. In addition, blood and urine tests are performed, including renal, thyroid, and lipid profiles, as well as anti-transglutaminase antibody, together with ophthalmologic, cardiologic, and neurologic evaluations. This general schedule is individualized according to each patient's characteristics and disease course.

The following parameters were recorded for the DKA episode: pH, bicarbonate (mEq/L), chloride (mEq/L), HbA1c (%), maximum creatinine (mg/dL) until resolution of the DKA, time of onset of AKI during DKA, and diuresis on admission. At the 8-year follow-up visit, age, sex, weight, height, body mass index (BMI) were recorded, as well as renal ultrasound, blood pressure, LDL cholesterol (mg/dL), creatinine (mg/dL), albuminuria, proteinuria, HbA1c (%), presence of retinopathy, neuropathy, celiac disease, and number of episodes of DKAs and AKIs (with their degree of severity). The mean HbA1c level from the onset to 8 years of disease progression was calculated, and the presence of comorbidities unrelated to T1D was recorded.

Definitions

- DKD: albuminuria (30-299 mg/24/h or albumin/creatinine ≥ 30 mg/g in 2 of 3 repeated morning urine samples over 3 to 6 months) and/or pathological proteinuria (≥ 300 mg/24/h or protein/creatinine > 0.2 mg/g in morning urine) and/or estimated GFR (eGFR) < 90 mL/min/1.73m^2 according to the Schwartz formula[10,11].
- DKA: blood glucose > 200 mg/dL, bicarbonate < 15 mEq/L, and/or pH < 7.3 according to the 2018 definition[9].
- The diagnosis and severity of AKI were defined according to the KDIGO criteria for serum creatinine, considering the maximum value during DKA[12]. According to its severity, AKI was classified as stage 1 when there was an increase in creatinine ≥ 0.3 mg/dL within 48 hours or 1.5-1.9 times the baseline creatinine value; stage 2 when the increase was 2-2.9 times the baseline value; and stage 3 when it was > 3 times the baseline value[12]. The KDIGO criterion of diuresis was not considered, as polyuria is a common finding in DKA, making it less reliable for the diagnosis of AKI[1]. Given the lack of knowledge of creatinine levels before the onset, a GFR of 120 mL/min/1.73m^2 was used as a reference to calculate the expected baseline creatinine[7,13].

- Hypertension: systolic and/or diastolic blood pressure ≥ 95th percentile for age, sex, and height[14].
- Overweight and obesity: BMI for age and sex > 1 or 2 standard deviations according to WHO tables, respectively[15].
- Hypercholesterolemia: LDL cholesterol >100 mg/dL[10].
- Hyperchloremia: plasma chloride > 75% of sodium levels[16].
- Hemoglobin A1c: the initial value and the mean since the onset were considered.

Statistical considerations

Descriptive variables are reported as median (interquartile range, IQR) since they did not have a normal distribution (Shapiro-Wilk test), and categorical variables are reported as the frequency of occurrence (percentages). Patients with and without DKD were compared using the Wilcoxon test, X^2 or Fisher's test, as appropriate. Variables with a p-value < 0.2 and clinical relevance were included in the multivariate analysis, the results of which are presented as odds ratios and 95% confidence intervals. Collinearity (variation inflation factors) and model goodness-of-fit (Hosmer–Lemeshow test) were evaluated. Significance level $p < 0.05$. Since all patients with DKD were eligible, the sample size was not calculated a priori; the power of the study was calculated a posteriori and considered adequate at > 80%. The software Statistix 7 and G-power 3.1.9.7 were used.

Results

Of 33 patients with DKD and a history of DKA at the onset, 17 were included (*cases*). Their visits took place between July 2022 and April 2023, so an additional 198 medical records of patients with T1D were reviewed, of which 42 were included (*controls*) (Figure 1).

The median age was 13 years (IQR 11-16), 28 (47.5%) were female, and the median age at the onset of T1D was 5 years (IQR 3-8). None had comorbidities unrelated to T1D, nor did they have already known renal dysfunction before the onset or abnormal ultrasound findings. In the patients included (n = 59) who presented with DKA at the onset of T1D, there were 22 events of AKI (37.2%); all were identified upon admission. In 13 patients (22%), it was grade 1, in 6 (10.1%) grade 2, and in 3 (5%) grade 3; all had polyuria (> 2 L/m²/day), none required dialysis, and renal function recovered with DKA treatment. Three patients had recurrent AKI (all grade 1) associated with DKA during follow-up.

The time from the onset of T1D to the development of DKD was 6.5 years[5-8]. No patient with DKD had a decrease in eGFR (median 132 mL/min/1.73 m²; IQR 109-150), 15 of them had pathological albuminuria (median 99 mg/g; IQR 68-120), and 2 had pathological proteinuria (protein/creatinine index 0.53 mg/g and 0.62 mg/g).

The cases had higher HbA1c values from the onset of the disease and greater frequency and severity (grades 2 and 3) of AKI than the controls (Table 1).

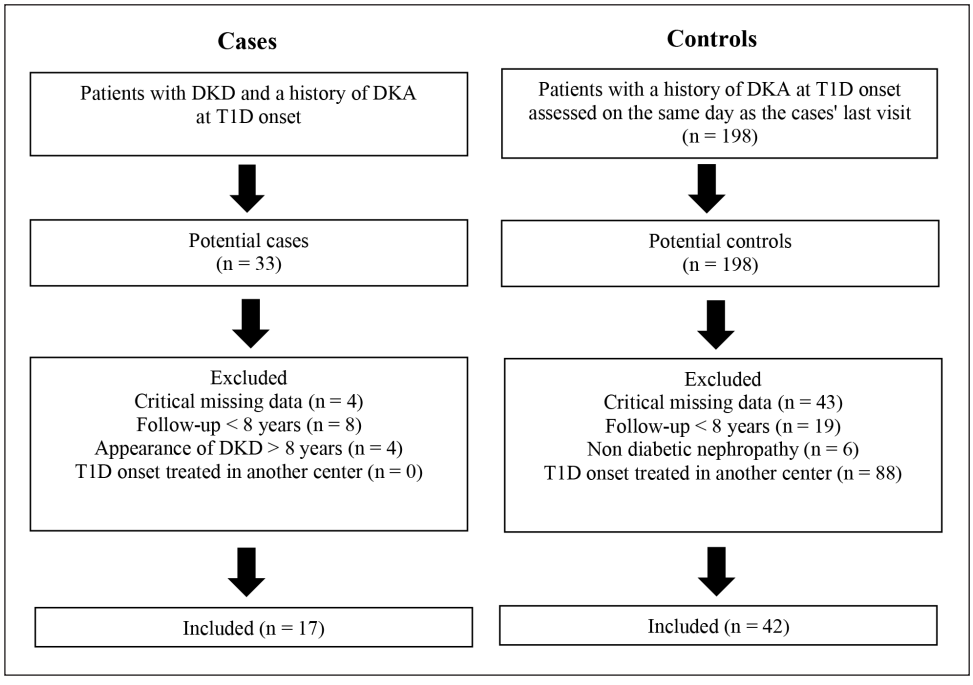

Figure 1. Flowchart illustrating the selection of study patients. DKD: diabetic kidney disease, DKA: diabetic ketoacidosis, T1D: type 1 diabetes, AKI: acute kidney injury.

Table 1. Parameters associated to the presence of diabetic kidney disease. Univariate analysis

Variable	Non-DKD (controls, n = 42)	DKD (cases, n = 17)	p-value
Age at enrollment (years), median (IQR)	12,6 (11-16)	15 (11,7-16)	0,22
Age at diagnosis of T1D, median (IQR)	4,6 (3-8)	7,4 (3,7-8)	0,17
Female sex (n, %)	20 (47,6)	8 (47)	0,96
HbA1c at T1D diagnosis, median (IQR)	10 (9-11,4)	11 (9-14)	0,57
Mean HbA1c since T1D diagnosis, median (IQR)	7,7 (7,1-8,6)	8,7 (8,1-9)	0,004
Hyperchloremia at DKA diagnosis (n, %)	25 (59.5)	9 (52,9)	0,64
Number of DKA episodes, median (IQR)	1 (1-1)	1 (1-2)	0,58
AKI occurrence (any stage) (n, %)	10 (23,8)	12 (70,5)	0,001
AKI stages 2 + 3 (n, %)	3 (7,1)	6 (35,3)	0,012
High blood pressure (n, %)	0 (0)	1 (5,8)	0,28
Hypercholesterolemia (n, %)	7 (17,5)	5 (29,4)	0,29
Overweight/obesity (n, %)	6 (14,3)	5 (29,4)	0,26
Neuropathy (n, %)	3 (7,1)	1 (5,8)	1,00
Retinopathy (n, %)	1 (2,4)	1 (5,8)	1,00
Celiac disease (n, %)	11 (26,2)	3 (17,6)	0,52

DKD diabetic kidney disease, T1D type 1 diabetes, HbA1c hemoglobin A1c, DKA diabetic ketoacidosis, AKI acute kidney injury.

Notably, 70.5% of patients with DKD (cases) had AKI at onset compared to 23.8% of those who did not develop DKD (controls) (Figure 2). In addition, the 3 patients with recurrent AKI developed DKD within 8 years of the onset. In the multivariate analysis, only a history of AKI remained associated with DKD (OR 5.4, 95% CI 1.18-24.6; p = 0.02) (Table 2). The post hoc power of the study was 93.7%.

Discussion

The main finding of this study was that having presented AKI during DKA at the onset of T1D was independently associated with DKD. Although our patients with DKD also had higher mean HbA1c since the onset, a known risk factor for microvascular complications[17], a history of AKI remained associated with DKD after adjusting for HbA1c. In fact, a single episode of AKI increased the probability of DKD more than fivefold.

Few pediatric studies have evaluated the consequences of AKI during DKA. Huang et al. reported an association between AKI during DKA and the onset of albuminuria in a cohort of 2345 children with T1D[7]. A similar finding was observed by Soltysiak in 18 patients[13]. It has also been reported that repeated or severe episodes of AKI increase the risk of CKD, suggesting a dose-dependent effect of AKI on the progression of damage[4]. Although in this study we only evaluated the association between AKI at the onset of T1D and renal outcome, notably, the three patients with repeated AKI developed DKD. Similarly, all three patients with grade 3 AKI developed DKD. Although the influence of the severity of AKI episodes was lost after multivariate analysis, this finding should be interpreted with caution, as it may not have been evident due to the limited sample size, since it is known that even mild episodes of AKI double the risk of progressing to CKD[4].

Considering that the prevalence of AKI during DKA reaches 47% and that it is a modifiable risk factor for DKD[1,5], strategies should be implemented to reduce this complication. Firstly, the fact that all our patients presented with AKI upon admission,

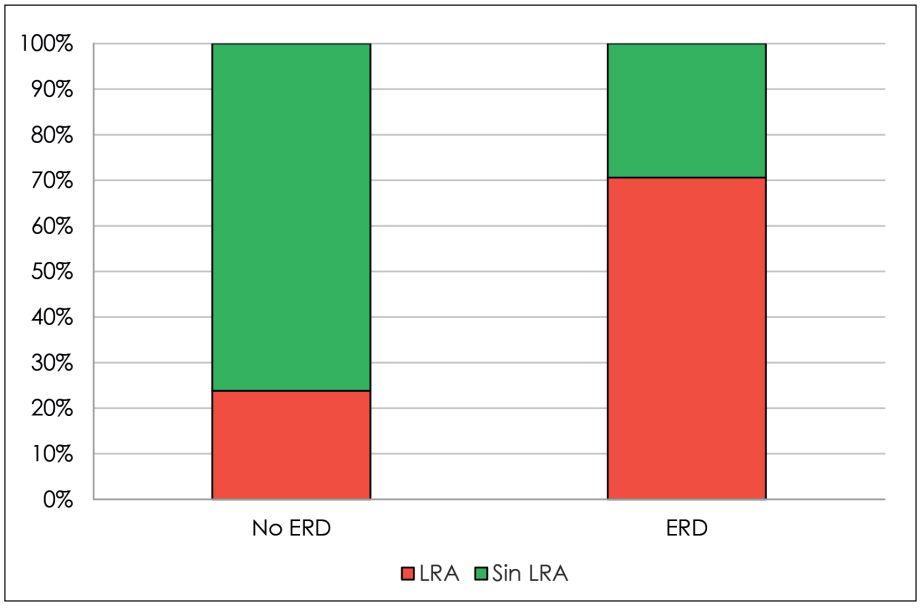

Figure 2. Development of DKD according to the presence or absence of AKI during DKA at T1D onset. *DKD* diabetic kidney disease, *AKI* acute kidney injury, *DKA* diabetic ketoacidosis, *T1D* type 1 diabetes.

Table 2. Parameters associated to the presence of diabetic kidney disease. Multivariate analysis

Variable	VIF	Odds ratio	95% CI	*p*-value
Age at diagnosis of T1D	1,06	1,19	0,92-1,56	0,18
Mean HbA1c level since diagnosis of T1D	1,07	1,47	0,88-2,46	0,13
AKI occurrence (any stage)	1,46	5,4	1,18-24,6	0,02
Severe AKI (stages 2 + 3)	1,49	2,95	0,41-20,93	0,27

Model X2 16.9, p = 0.002
Hosmer–Lemeshow test p = 0.34
Predicted 81.4 %

VIF variance inflation factor, CI confidence interval, HbA1c hemoglobin A1c, T1D type 1 diabetes, AKI acute kidney injury.

although it is difficult to establish at what stage they were, since they all presented with polyuria, indicates that efforts to prevent it would consist of avoiding the onset of DKA. Indeed, it has been reported that episodes of AKI are more frequent among patients who develop DKA compared to those who do not (83% vs. 35%)[18]. Therefore, more information should be provided to the population about the cardinal symptoms of T1D to facilitate early diagnosis and reduce the risk of DKA, both in individual care and through public campaigns[5]. Furthermore, given the high prevalence of AKI during episodes of DKA[5,6], treating physicians should actively look for this complication, as its recognition during DKA is often difficult due to osmotic polyuria and lack of knowledge of previous creatinine values[1,7]. Additionally, patients with T1D should also be educated on the prevention of recurrent episodes of DKA and other events unrelated to T1D, such as dehydration, prolonged fasting, or surgery, which can potentially trigger AKI[1].

The treatment of AKI must be individualized, balancing adequate rehydration to reverse kidney damage without increasing the risk of cerebral edema[1]. The recommended fluid is normal saline, although it may cause hyperchloremia and, due to the vasoconstrictive effect of chlorine, induce AKI during DKA[16]. Although solutions with lower chloride content emerged as an alternative approach to avoid hyperchloremia, their use did not achieve better results[16]. In our patients, the frequency of hyperchloremia was similar between patients with and without DKD; however, it should be noted that, due to the study design, the comparison was not made between patients with and without AKI.

This study has several limitations that should be mentioned. Due to the fixed maximum number of patients with DKD and the retrospective nature of the

study, with a lack of data in some cases, the sample size was limited. The sample size calculation, considering that the proportion of patients with T1D in childhood who develop DKD ranges from 9% to 26%[10] and that pediatric studies in other pathologies revealed that the prevalence of CKD after an episode of AKI is approximately 40%[19], 59 cases and 59 controls would have been required to demonstrate a 1.56 risk of developing post-AKI albuminuria associated with DKA[7]. Although our sample size was smaller, the post-hoc power of the study was adequate and allowed us to demonstrate a significant association between AKI and DKD, although we must acknowledge that the width of the confidence intervals indicates low precision of our findings. Therefore, prospective studies with a larger number of patients are needed to confirm these preliminary results. Another limitation was the lack of matching of cases and controls. Despite this, both groups were comparable in all measured variables, except for the mean HbA1c since the onset of T1D, which was adjusted in the multivariate analysis. In addition, the lack of knowledge of baseline creatinine may have affected the diagnosis and staging of AKI. To reduce this situation, as in other pediatric studies on AKI, we assumed that our patients had a baseline GFR of 120 mL/min/1.73m² to calculate the expected baseline creatinine[7,13]. Finally, as the study was conducted at a single center, the generalizability of its results may be limited; however, this ensures that patients were treated with the same protocol and prevents misdiagnosis of DKD based on transient episodes of albuminuria.

Conclusion

Presenting AKI during DKA at the onset of T1D increased the probability of presenting DKD at 8 years of disease progression more than 5-fold, regardless of the degree of metabolic control of the disease. Interventions to prevent DKA and, consequently, AKI at the onset of the disease could reduce the risk of DKD.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: This study was approved by the respective Research Ethics Committee. The authors state that the information has been obtained anonymously from previous data.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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