

Diabetic ketoacidosis with acute kidney injury in prepubertal children: a report on two cases

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Type 1 diabetes mellitus is a result of autoimmune damage, in which environmental factors are thought to trigger the autoimmune destruction of pancreatic β -cells.^{1,2} Worldwide, an estimated 65,000 children under 15 years of age develop type 1 diabetes mellitus each year.³ Approximately 30% of children who present with newly-diagnosed type 1 diabetes have diabetic ketoacidosis (DKA).⁴ Himawan *et al.* reported a DKA prevalence of 43.6% in girls.⁵ The long-term effects of diabetes mellitus include retinopathy, chronic kidney disease (nephropathy), neuropathy, and dyslipidemia.²

In Indonesia, DKA is often unidentified and therapy inadequate, due to several factors such as a dearth of health care facilities in remote areas, a culture of avoiding doctors, financial constraints, and regulations governing access to care. These factors may lead to late diagnoses and even fatalities. The DKA occurs in 10-70% of children with type 1 diabetes mellitus and has a significant risk of mortality due to cerebral edema and other potential complications such as acute renal failure (ARF)/acute kidney injury (AKI).⁶ Asl *et al.* in Iran, reported that 4.7% of children with DKA had acute renal failure.⁷ Acute kidney injury, though it rarely develops in DKA patients, may be severe and potentially life-threatening in critically ill children.⁶ The AKI is defined as a syndrome where the kidneys fail to adequately regulate electrolytes, as well as acid-base and fluid homeostasis, with concomitant reduction in glomerular filtration rate

(GFR).⁸ The mortality rate of AKI is up to 60% in critically ill children, and influenced by the severity of the primary diseases, organ dysfunction, and stage of AKI.^{9,10} Classification of AKI are determined according pediatric RIFLE (pRIFLE) criteria.¹¹

Here, we present two cases of prepubertal girls with poorly controlled type 1 diabetes mellitus, who were diagnosed with DKA and AKI. [Paediatr Indones. 2016;56:361-8. doi: 10.14238/pi56.4.2016.361-8].

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The cases

Two patients who had been diagnosed with DKA were evaluated at Eka Hospital, Pekanbaru. Both

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Table 1. Clinical characteristics of the patients with DKA and AKI

Characteristics	Case 1	Case 2
Age	8y 8m	9y 5m
Gender	F	F
BMI, kg/m ²	11.11	16.71
Chief complaint	Unconsciousness	Unconsciousness
Urine output, mL/kg/hr	0.06	0.9
Type of dialysis	CAPD	CAPD
Blood gas analysis		
pH	6.99	7.1
HCO ₃	4.6	6.9
Glucose level, mg/dL	233	679
Urinalysis		
Protein	Negative	Positive
Glucose	Negative	Positive
Ketone	Negative	Positive
Glomerular filtration rate, mL/min		
Initial	20	18.89
Pre-CAPD	21.85	11.27
Post-CAPD	227.59	129.29

patients were girls, aged 8-9 years, with clinical characteristics and laboratory findings shown in **Tables 1**. Evaluations included initial blood gas analyses, blood glucose measurements, HbA1c, urinalysis, urea, creatinine, GFR, clinical features, and dialysis mode needed.

Case 1

An eight year eight month-old girl was referred to our hospital with a chief complaint of decreased level of consciousness for the two days prior to admission. Three days before admission, she was in a convulsive state and was admitted to a rural hospital. She had been diagnosed with type 1 diabetes mellitus (DM) in 2009, but had irregular follow-up visits.

Upon presentation, the patient had a Glasgow coma scale (GCS) of 5. Vital signs were as follows: pulse 129 beats/min, respiratory rate 20/min with 94% oxygen saturation, temperature 35.1°C, and blood pressure 83/48 mmHg. Weight and height were 16 kg and 120 cm, respectively, BMI was 11.11 kg/m². Her height was below the 5th percentile, with nutritional status (weight/height) classified to be wasting, according to the 2000 WHO-CDC reference charts and Waterlow criteria.^{12,13} Palpebral and peripheral edema, rales on both lung fields, and ascites were

present.

The initial laboratory evaluation revealed complete blood count results of: Hb 11.1 g/dL, hematocrit 31.7%, white blood cell (WBC) 23,000/ μ L, platelets 190,000/ μ L, and erythrocyte sedimentation rate 35 mm/hour. Blood gas analysis results were pH 6.99, P O₂ 136 mmHg, P CO₂ 16.2 mmHg, base excess (BE) -28, bicarbonate 4.0 mmol/L, total CO₂ 5 mmol/L, potassium 2.7 mmol/L, and ionized calcium 1.38 mmol/L. The urea level was 115 mg/dL, creatinine level 1.95 mg/dL, and blood glucose 233 mg/dL. HbA1c level was found to be 15% and albumin was 2.6 g/dL. Liver enzymes were normal. Urinalysis results were as follows: 4+ occult blood, negative protein, negative glycosuria, negative ketonuria, erythrocytes in urine sediment of 154.1/ μ L, WBC 78.3/ μ L, and 3+ leukocyte esterase.

The patient received furosemide, bicarbonates, dopamine, and dobutamine. She was started on a regular insulin drip at 0.1 U/kg/hr. Imipenem and cilastatin were initiated, as *Rhizobium radiobacter* was isolated from sputum and *Stenotrophomonas maltophi* was isolated from urine. Fluconazole was also given after cultures showed *Candida albicans* growth.

Upon admission, this patient developed oliguria with a urine output of 0.06 mL/kg/hour, along with abnormal urea and creatinine levels (119 mg/dL and 3.02 mg/dL, respectively) as well as decreased GFR (20 mL/min). Hence, we decided to perform continuous ambulatory peritoneal dialysis (CAPD). After CAPD, her urea level decreased to 72 mg/dL and creatinine level decreased to 1.09 mg/dL. Urine output was between 0.08-0.6 mL/kg/hour, with GFR of 20-29 mL/min.

Mental status, metabolic acidosis, and respiratory failure had improved. Palpebral edema was decreased, and edema of the abdomen and all extremities was not detected. The patient tolerated the CAPD well, and her lungs were clear. Albumin and ampicilin were given intravenously. On the 5th day of hospitalization, she responded to commands and was aware of her location and people around her. She was weaned off hemodynamic and ventilatory support and transferred to the high care unit (HCU) after 5 days in the PICU. As her mental status recovered, she transitioned off the insulin infusion to a subcutaneous regimen of premixed insulin (*NovoMix*®: 30% rapid-acting and 70% intermediate-acting insulin) twice per day.

Intravenous metronidazole and KCl were initiated.

On the 11th day of hospitalization, the patient's blood pressure was 120/76 mmHg. Abdominal ultrasonography revealed bilateral nephromegaly. She had an episode of high blood pressure starting on the 15th day of hospitalization. Her blood pressure ranged between 101/69 and 138/90 mmHg, and she was given angiotensin-converting enzyme (ACE) inhibitor (*Captopril*®) at a dose of 3 mg twice per day.

The CAPD was discontinued at the 30th day of hospitalization after the patient's blood pressure, and levels of urea and creatinine improved. She had episodic hyperglycemia following discontinuation of the CAPD, up to 200 mg/dL (**Figure 1**). The treatment for hyperglycemia consisted of subcutaneously premixed insulin (*NovoMix*®: twice per day at 6 am (14 units) and 6 pm (8 units), short-acting human insulin (*Actrapid*®: 8 units), and rapid-acting insulin (*NovoRapid*®: 5 units). At day 33 of hospitalization, we changed the treatment for hyperglycemia to long-acting insulin (*Lantus*®) at 7 am (10 units) and subcutaneously premixed insulin (*NovoMix*®) twice per day, at 1 pm (5 units) and 6 pm (5 units).

At day 39 following presentation and upon completion of parental education, the child was discharged and parents were instructed to continue the insulin regimen three times daily, with 1.3 UI/kg of

long-acting insulin (*Lantus*®) at 7 am (12 units) and subcutaneously premixed insulin (*NovoMix*®) twice per day at 1 pm (5 units) and 6 pm (5 units).

On her first follow-up, she was clinically active, had good appetite, adequate urine output, and no fever. Her recorded blood glucose were 105-283 mg/dL. She continued to follow her insulin regimen. Unfortunately, this patient did not return for her subsequent 2-week follow-up.

Case 2

A nine year five month-old girl presented to our hospital in a depressed consciousness/comatose state since 14 hours prior to admission, and a diagnosis of tuberculous meningitis. Her temperature elevated after unconsciousness. One day prior to admission she looked faint with episodes of shortness of breath and complaints of abdominal pain. One week prior to admission, she complained of nocturnal enuresis. Six months prior to admission the patient appeared to be losing weight. Her past medical history included lymph node tuberculosis and she had taken tuberculosis medications for 6 months. Her father had also been diagnosed with diabetes 1 year previously, with blood glucose \geq 500 mg/dL.

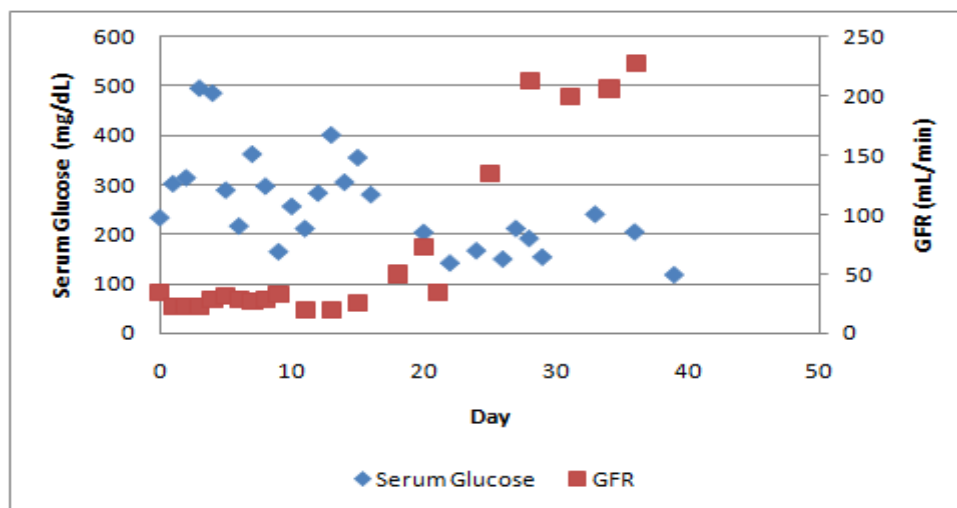


Figure 1. Case 1 serum glucose and GFR during hospitalization (pre- and post-insulin regimen administration and CAPD procedure)

Upon admission, her weight and height were 30 kg and 134 cm, respectively. Her BMI was 16.71 kg/m² and her height was below the 50th percentile, with a normal nutritional status (weight/height), according to the 2000 WHO-CDC reference charts and Waterlow criteria.^{12,13} The initial assessment revealed blood pressure 74/40 mmHg, pulse rate 150 beats/min, respiratory rate 30/min with Kussmaul breathing, temperature 40.7°C, oxygen saturation of 92%, and dry mucus membranes. The neck was supple without lymphadenopathy, and she had normal findings on lung and cardiac examinations, consistent with sinus tachycardia and no murmurs. Peripheral and palpebral edema were not detected. The patient's abdomen was flat, soft, non-distended, and without hepatosplenomegaly. Neurological examinations were normal.

Biochemistry results upon admission showed the following: blood gas analysis pH 7.1, Pa CO₂ 23.4 mmHg, Pa O₂ 82.7 mmHg, oxygen saturation 85.9%, chloride 112 mmol/L, bicarbonate 6.9 mmol/L, total CO₂ 7.5, and BE -22.3. Complete blood count results were Hb 14.8 g/dL, hematocrit 45.4%, WBC 24,100/ μ L, platelets 175,000, and erythrocyte sedimentation rate 6 mm/hour. Blood glucose was 679 mg/dL, HbA1 9.2%, urea 71 mg/dL, creatinine 3.9 mg/dL, GFR 18.89 mL/min, and albumin 4 g/dL. Urinalysis results were

1+ protein, 3+ glycosuria, 4+ blood, 3+ ketonuria, erythrocytes in urine sediment 44.5/ μ L, WBC 20.1/ μ L, cylinder urine 6.91/ μ L. The patient's liver enzymes were normal and blood cultures showed no bacterial growth.

In the PICU, the patient was unconscious with the appearance of soporous-coma and bleeding from the mouth. Her vital signs were blood pressure 123/64 mmHg, pulse rate 143 beats/min, body temperature 37°C, and respiratory rate 26/min. The patient was given a short-acting insulin drip (regular insulin), dopamine, dobutamine, as well as intravenous furosemide, ranitidine, and cefuroxime. On the second day of hospitalization, patient awareness and metabolic acidosis improved, but she was still somnolent. Her blood pressure increased to between 128/93 and 140/96 mmHg. *Captopril*® (10 mg, 3 times/day) were prescribed. On the 6th day of hospitalization, the patient developed oliguria, with diuresis of 0.3 mL/kg/hour. We performed CAPD on the patient. Her blood pressure improved to within a range of 120/80 mmHg and 108/69 mmHg. On the 7th day of hospitalization, the patient was fully awake with a GCS score of 15. Diuresis was still 0.3 mL/kg/hour. Blood glucose was 212 mg/dL. The patient was given subcutaneous rapid-acting insulin (*NovoRapid*®, 5 units) before eating. On the 11th day

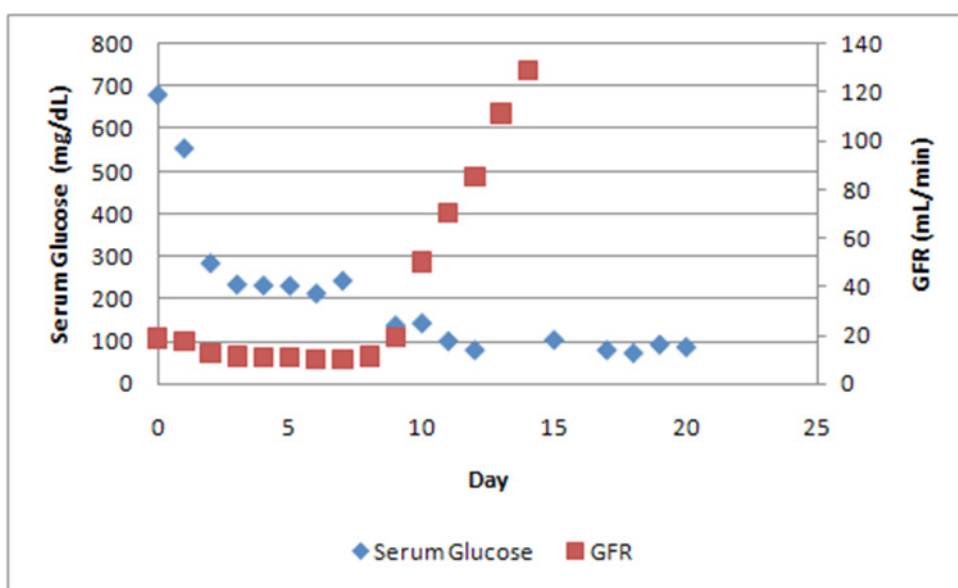


Figure 2. Case 2 serum glucose and GFR during hospitalization (pre- and post-insulin regimen administration and CAPD procedure)

of hospitalization, diuresis improved, with a urine output of 2.3 mL/kg/hour. The patient's lipid profile results were low density lipoprotein (LDL) 120 mg/dL, high density lipoprotein (HDL) 35 mg/dL, total cholesterol 169 mg/dL, and triglycerides 179 mg/dL. Urea level was 65 mg/dL and creatinine level was 1.04 mg/dL. The GFR was 70.86 mL/min. The patient's hypertension resolved. We discontinued the CAPD cycle and short-acting insulin drip (regular insulin). On day 17 of hospitalization, her DKA and acute kidney injury resolved, and blood glucose was stable. On the 20th day of hospitalization, rapid acting insulin (*NovoRapid*®) was given twice per day, at 4 units before lunch and 3 units before dinner. Patient vital signs were stable. **Figure 2** shows the serum glucose levels and GFR during hospitalization. At the 27th day of hospitalization, the patient was discharged, as her type 1 diabetes was considered to be well-controlled, with instructions to return as an outpatient. Her medications included subcutaneous rapid-acting insulin given twice per day (4 units before lunch and 3 units before dinner), but if her blood glucose was < 80 mg/dL, then *NovoRapid*® was not to be given. Cefadoxril syrup was continued.

On her follow-up visit, the patient was healthy and physically active with good appetite and adequate urine output. Her weight had increased by 1.5 kg. Therapy comprised of subcutaneous rapid-acting insulin (*NovoRapid*®, twice per day, 4 units before lunch and 3 units before dinner). A laboratory work-up showed 6.40% HbA1c. Urinalysis and complete blood count results were normal.

Discussion

These two DKA cases were from a rural area, and from families with low socioeconomic status. For any child presenting with impaired consciousness and/or acidosis, diabetes mellitus should be considered in the differential diagnosis.

Most children and adolescents with type 1 diabetes mellitus present with a several-week history of polyuria, polydipsia, polyphagia, and weight loss with hyperglycemia, glycosuria, ketonemia, and ketonuria. However, obtaining a classic history in younger children with diabetes is difficult.^{4,14} Furthermore, these symptoms do not appear until

about 80% of the pancreatic islets have been destroyed.¹ Between 25% and 30% of children who present with newly diagnosed type 1 diabetes are ill with DKA and require treatment in an intensive care unit.^{4,14} Our first patient had been diagnosed with type 1 diabetes 2 years before this hospitalization, while diabetes in the second patient was not diagnosed until the laboratory workup was done. Both our patients required treatment in the PICU, and had a chief complaint of unconsciousness. DKA tends to be more common in younger patients who have a shorter duration of symptoms.^{14,15} The age of our patients was between 8 and 9 years.

The biochemical criteria for DKA diagnosis published by the *International Society for Pediatric and Adolescent Diabetes* (ISPAD) includes hyperglycemia (blood glucose level >11 mmol/L), acidosis (venous pH value <7.3 and serum bicarbonate level <15 mmol/L), ketonemia, ketonuria, and dehydration due to hypoinsulinemia.^{14,16,17} Classification of DKA is as follows: mild DKA for venous pH <7.3 and/or bicarbonates <15 mmol/L; moderate DKA for pH <7.2 and/or bicarbonates <10 mmol/L; and severe DKA for pH <7.1 and/or bicarbonates <5 mmol/L.^{18,19} Both of our patients were diagnosed with DKA. The major signs of DKA are nausea, vomiting, abdominal pain, and acidosis.^{14,15} Seth *et al.* reported that nausea and vomiting were the most common symptoms (63.33%), followed by abdominal pain (43.33%).²⁰ Case 1 was classified as having severe DKA; case 2 was classified as having moderate DKA. Late diagnosis and inadequate medical facilities can contribute to the manifestations of severe DKA, coma, and even death. The mortality rate from DKA was reported to be 3.4% and above, in several studies.^{14,17}

Both of our patients were female. A previous study reported the prevalence of DKA to be 4.6 to 8 per 1,000 patients with type 1 diabetes each year, and higher in female patients.²¹ Himawan *et al.* also reported a DKA prevalence to be 43.6% in female patients (17 patient) and 33.3% in male patients (13 patient), presented in early diagnosis of DKA, the prevalence was 86.7% in 26 patients and many of them were female.⁵ Alphonsus and Emeka reported from 37 patients, the males:females ratio was 1:1.5.¹⁸

Factors that precipitate DKA in children and adolescents include emotional stress, infection, missed insulin injection, trauma, pancreatitis,

and poor compliance to medication in patients with known diabetes.^{15,17} Infection is the most common precipitating cause of DKA, occurring in 30-50% of cases.¹⁴ One patient had missed insulin injections and poor compliance to medication, and the other patient had elevated temperature and unconsciousness, with a differential diagnosis of tuberculous meningitis.

The DKA was resolved in both patients. The first patient (pH 6.99; severe DKA) was treated with bicarbonate and dobutamine support for hypotension. The use of bicarbonate is controversial, as there is no evidence of beneficial effects on patients with a pH between 6.9 and 7.1.¹⁷ Bicarbonate should only be considered to improve cardiac contractility in patients with severe DKA (pH < 6.9) and with circulatory failure. The effect of using bicarbonate may, paradoxically, cause acidosis of the central nervous system and contribute to cerebral edema. Hypokalemia may also occur, due to the rapid correction of acidosis upon using bicarbonate.¹⁴ The management of DKA requires frequent monitoring, correction of hypovolemia, acidosis and hyperglycemia, replacement of electrolyte losses, and a search for the precipitating cause. During DKA, a depletion of total potassium occurs, where potassium remains in the plasma due to the lack of insulin.^{14,15} Potassium replacement is necessary because hypokalemia is the most life-threatening electrolyte imbalance and predisposes patients to cardiac arrhythmias.¹⁵ Early addition of potassium is essential even if serum potassium is normal, because insulin will drive glucose and potassium into the cells.¹⁴

In the emergency room, we chose to administer fluids only during the first hours for dehydration. Insulin infusion should not be started until 1 hour after starting fluid replacement therapy.^{17,22} Early administration of insulin (within the first hour of fluid replacement) could be lethal, due to a rapid shift in osmolality and influx of potassium from plasma into cells, which increases the risk of cardiac and respiratory failure, as well as cerebral edema.^{17,22} According to the guidelines for insulin treatment of DKA, small doses of regular insulin (human insulin/short-acting insulin) for continuous intravenous administration are the therapy of choice for pediatric DKA (0.1-0.05 U/kg/h), and an IV insulin bolus should not be given.^{4,17,22} It is very important that insulin infusions not be stopped before the acidosis is corrected, as insulin is required to switch off ketone

production.¹⁴

The AKI remains a significant contributor to the morbidity and mortality of critically ill infants and children and occurs more frequently in intensive care units (ICUs), especially in patients with multi-system organ failure.^{8,23} The etiology of AKI associated with DKA is probably multifactorial, most likely due to hypovolemia and hypotension.⁶ AKI is frequently associated with severe DKA on ICU admission.²⁴ Only one of our patients had severe DKA, while the other had moderate DKA, but both had AKI. According to the guidelines of Chantler and Barrat, AKI is diagnosed when the serum creatinine concentration is greater than the normal value for the age and height of patient.^{25,26} In patients with AKI, 0.5% require dialysis. Peritoneal dialysis is an advantageous modality for renal replacement therapy (RRT) in AKI.²³ Our patients had several indications for dialysis including oliguria/anuria, intractable metabolic acidosis, fluid overload, and hypertension. We used the pediatric RIFLE (pRIFLE) classification to assess for AKI and to evaluate kidney injury on admission and at subsequent times.^{11,27,28} The pRIFLE criteria are risk, injury and failure, based on decreased in estimated creatinine clearance (eCCL) and urine output according to body weight.²⁸ The estimated creatinine clearance was calculated according to the Schwartz formula for glomerular filtration rate (GFR).²⁹ Initial AKI treatment was based on correction of hypovolemia by fluid infusion.²⁴

The urinalysis of the first patient was negative for protein, but that of the second patient was positive for protein (1+ protein). The prevalence of persistent microalbuminuria (MA) in children with type 1 diabetes mellitus was reported to be 4 - 20%, depending on variables including age, glycemic control, and diabetes duration. The occurrence of MA is very rare before puberty and its prevalence is low for those with diabetes duration of less than 3-5 years.^{22,30,31}

Most children with type 1 diabetes should be considered at low risk of dyslipidemia, and screening should be targeted at those >12 years of age as well as younger children with specific risk factors.²² Hyperlipidemia and high blood pressure typically develop once MA has occurred.³⁰ Insulin deficiency increases free fatty acid (FFA) and amino acid release from adipose tissue and muscle.

Elevated free fatty acid (FFA) taken up by the liver leads to increased production of (VLDL), which causes hypertriglyceridemia.³² Once dyslipidemia is diagnosed in children with type 1 diabetes, the dyslipidemia should be treated per lipid guidelines for adults with diabetes.²²

Blood pressure was elevated in our two patients. Hypertension in diabetes is associated with expanded plasma volume, increased peripheral vascular resistance, and low renin activity.³³ Hypertension is defined as an average systolic or diastolic blood pressure $\geq 95^{\text{th}}$ percentile for age, sex, and height measured on at least 3 separate days.^{4,34} We used ACE inhibitors (*Captopril*®) for hypertension. An ACE inhibitor is the drug of choice in hypertensive children and adolescents with type 1 diabetes. It is also safe and efficacious. The second-line drugs include calcium channel inhibitors, alpha-receptor blockers, or low-dose thiazides.^{4,33} The ACE inhibitors have an anti-hypertensive effect by delaying the progression of the diabetic nephropathy (DN) by normalizing glomerular capillary pressure independently, reducing the progression of both MA and overt proteinuria in hypertensive diabetics, and significantly reducing the progression from MA to normoalbuminuria.^{30,31} After starting *Captopril*®, the blood pressure normalized with the metabolic control of hyperglycemia. Blood pressure and microalbuminuria screening is strongly recommended for preventing diabetic nephropathy.³⁰

The HbA1c is the best laboratory parameter for estimating glycemic control in diabetic patients. The recommended objectives are to maintain HbA1c $< 7.5\text{--}8.0\%$, fasting blood glucose concentration < 140 mg/dL, and 2-hour postprandial blood glucose concentration < 200 mg/dL.³⁵ Glycemic targets for children aged 6-12 years (prepuberty) should aim for an HbA1c target of $\leq 7.5\%$.²²

Our AKI patients received CAPD. Both had renal failure according to pRIFLE assessment. In some European countries, hemodialysis (HD) is preferred for children over the age of five years, while peritoneal dialysis (PD) is offered to younger children, especially those under the age of two years or weighing less than 10kg.³⁶ The modality of choice is also determined by a variety of factors, including provider preference, available institutional resources, dialysis goals, and the specific advantages or disadvantages of each

modality. Peritoneal dialysis has been the primary renal replacement therapy (RRT) modality. Most clinicians have a relatively greater comfort level with employing this therapy. Peritoneal dialysis has also been effective for children with AKI because it can be administered quickly and easily in all settings, even for the most unstable patients, as the PD catheter can be inserted at bedside with minimal cost.²⁶ PD is also considered to be better in terms of quality of life, psychosocial adaptation, higher levels of subjective well-being, ease of vascular access, and preservation of residual renal function (RRF).³⁷ Alkan *et al.* and Flynn reported that Peritoneal dialysis remains an effective modality for the management of pediatric AKI.^{38,39} Complications of PD include bladder and bowel perforation, along with bleeding issues related to the procedure.⁸ Peritonitis was not seen in our patients.

In conclusion, we report on two prepubertal children who are diagnosed with DKA. We would like to highlight the need for early recognition of diabetes in children by general practitioners and pediatricians, in order to prevent DKA and reduce its fatal complications, especially in critically ill children with AKI. We regard CAPD as an effective treatment for renal failure in children with AKI.

Conflict of interest

None declared.

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