Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Mixed diabetic ketoacidosis and hyperosmolar hyperglycemic state in children: a retrospective cohort study of clinical characteristics, complications, and fluid management

Amir Saeed
Shiraz University of Medical Sciences
Fatemeh sadat mirrashidi
fatemeh.mirrashidi@gmail.com
jiroft university of Medical sciences
Amir Naghshzan
Shiraz University of Medical Sciences

Research Article

Keywords: complications, Diabetic ketoacidosis (DKA), diabetes mellitus (DM), hyperglycemic hyperosmolar state (HHS)

Posted Date: September 4th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10704414/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Additional Declarations: No competing interests reported.

Abstract

Introduction

DKA and HHS are the severe complications of diabetes mellitus. Some patients with DKA, but they also have plasma glucose (>600 mg/dL) and increased serum osmolarity(> 320 mOsm/kg); these patients are defined as mixed DKA-HHS. This study aims to assess the frequency of mixed DKA-HHS and define the characteristic laboratory data, complications, and prognosis of these patients.

Materials and Methods

This is a retrospective observational cohort study on patients had biochemical criterion for mixed DKA-HHS. First, those with DKA criteria including PH<7.3, plasma glucose> 200 mg/dL, bicarbonate <15, and ketosis were evaluated. Next step, those whose effective osmolarity was > 320 mosm/L and their plasma glucose was >600 mg/dL were selected. Those patients admitted to the pediatric intensive care unit (PICU) of Namazi Hospital from March 2017 to June 2021 enrolled in this study.

Results

During this study, 453 pediatric patients with DKA treated at our hospital, 144 required PICU admission. Nine patients met criteria for mixed DKA-HHS, representing 1.99% of all DKA cases and 6.25% of PICU DKA admissions. that all were female; the age beetwin 14 months old-15 years old.Mixed DKA-HHS was the first presentation of DM in four patients. Acute kidney injury (AKI) was observed in four patients, and rhabdomyolysis in one patient as a complication of this disease.

Conclusions:

Mixed DKA-HHS requires modification of standard DKA management because of the additional risks associated with severe hyperosmolality and dehydration., so early diagnosis is crucial for appropriate management and prevention of complications.

Introduction

Diabetic ketoacidosis (DKA) is one of the severe diabetes mellitus (DM) complications, characterized by hyperglycemia (plasma glucose more than 200 mg/Dl), venous PH less than 7.3, and ketonemia or moderate to severe ketonuria(1). Hyperglycemic hyperosmolar state (HHS) is also considered another diagnostic and treatment challenge in DM patients usually present with extreme hyperglycemia (plasma glucose more than 600 mg/dL), effective serum osmolality greater than 320 mOsm/kg, venous PH greater than 7.25, and absence of minimal ketosis (1).

HHS has a high mortality and morbidity rate in elderly patients with type 2 DM; however, it has not been significantly recognized in young patients (2). Although these two have distinct diagnostic criteria, they may coincide, upbringing some treatment dilemmas for practitioners. The following condition is currently diagnosed with the mixed HHS and DKA; that is, the patient has arterial PH less than 7.3 and bicarbonate less than 15 and at the same time has plasma glucose greater than 600 mg/dL and osmolality more than 320 mOsm/kg(1, 3).

The incidence of DKA in known diabetic children is 0.7% (4) to 92.1%(5). The incidence rate of mixed type is about 14% of pediatric patients with hyperglycemia (6). Although the incidence rate of HHS and mixed DKA-HHS is lower than isolated DKA, the risk of complications such as rhabdomyolysis and thrombosis is higher in them(2).

We conducted this study to determine the frequency, characteristics, complications, and prognosis of the pediatric patients admitted in pediatric intensive care of Namazi Hospital in Shiraz, Iran, with the impression of mixed types of DKA-HHS.

Materials and Methods

This is a retrospective observational cohort study on DM patients with DKA-HHS admitted to the pediatric intensive care unit (PICU) of Namazi Hospital from March 2017 to June 2021.

Our PICU is an academic referral unit with 18 active beds that cares for over 400 pediatric patients annually.

All pediatric patients aged less than 18 years old with DKA-HHS criteria included (PH < 7.3, plasma glucose > 200 mg/dL, bicarbonate < 15, ketosis, and effective osmolarity more than 320 (mosm/L). Effective osmolality (mOsm/kg) calculated as 2 × (plasma Na) + plasma glucose (mmol/L)(2 x (plasma Na) + Glucose (mg/dL) / 18). Those who had insufficient data for diagnosis were excluded.

Demographic characteristics, past medical history, familial history of DM, the first clinical presentation, the course of hospital stay, prognosis, and laboratory data obtained from medical records through four years (March 2017 to June 2021). Complications related to mixed DKA-HHS such as rhabdomyolysis, acute kidney injury (AKI), thrombosis, and altered level of consciousness were evaluated. AKI is defined as\ increase in the serum creatinine equal to or more than 1.5 times that of baseline related to disease or has occurred within the previous seven days (7).

Results

Of the total of 144 pediatric patients admitted with DKA in PICU(it was 453 patients in pediatric ward of our Hospital) through that time, nine patients(1.98% of total;,6.2% of PICU'S) had met the criteria for mixed DKA-HHS; all the patients were female (the characteristics and the initial laboratory data shown in Table 1). Five patients were known cases of DM who used insulin, but none of them had positive familial history. Body mass index (BMI)-for-age percentile was > 97% in one patient (case NO. 1) and 92%(overweight) in case NO.2 others were in normal range. Hypophosphatemia was found in five patients which of them, three patients were the new cases of DM, and two patients were known cases of DM for more than three years. Three patients were intubated (cases NO 1 ,3,and 9) due to decreased level of consciousness; the course of intubation time in case 1 was seven days, it was two days for case 3,and 3 days for the last one.

Table 1
The patients' characteristics and the first laboratory data

Age	Case NO.1	Case NO.2	Case NO .3	Case NO.4	Case NO.5	Case NO.6	Case NO.7	Case NO.8	Case NO.9
	15	14	10	8	9	14 months	11	14	13
Known case of DM	+	-	+	-	+	-	-	+	+
Weight(KG)	72	59	22	19	25	11	38	42	45
BMI(kg/m^2)∞	28.1	25.5	13	13.1	16	15.9	16.8	16.2	20.4
GCS**	8/15	13/15	7/15	13/15	13/15	14/15	12/15	13/15	6/15
ABG* PH	6.95	7.09	6.9	6.97	7.02	6.88	7.11	6.8	6.82
HCO3	3.2	3.8	2.2	4	5.8	2.4	5.8	1.8	1
Effective osmolality (275–295 mmol/kg)	346.5	334	343.8	349	333	370	369	373	336
BUN(mg/dl) +	48	42	23	24	16	8	38	52	60
Creatinine	2.6	1.5	1.2	0.8	1.1	0.73	1.8	1.9	1.6
Plasma glucose	730	651	970	710	674	842	958	812	685
Amylase	210Ω								
Chloride (96 -106MEq/L)	131	106	111	104	108	114	102	114	108
Magnesium (1.7 to 2.2 mg/dL)	2.4	1.8	1.7		2.1	1.5	1.9	2	1.6
Phosphorus ©	1.9	7.5	3.5	1.6	2.8	2.2	3.1	2	3.2
Calcium (8.5 to 10.5 mg/dl)	10	10.6	8	8.3	9.8	8.2	9.2	8.8	8.2
Sodium (135–145 mEq/L)	153	149	145	155	148	162	158	162	149
Potassium (3.5–5.5 mmol/L)	6.8	5.2	5.8	3.2	5	3.3	5.4	5.6	4.8
CPK ≠ (22 to 198 U/L)	10460	161	97	39	48	72	52	85	125
Intubation	+	-	+	-	-	-	-	-	+
%Fluid deficit which was given	14	15	14	12	12	16	15	15	14

*ABG:arterial blood gas,+ blood urea nitrogen, ∞body mass index,≠ creatinine phosphokinase,** Glasgow coma scale ©Normal range; Infant:4.8–7.9 mg/dl ,pediatric:3.4–6.2,adult:2.7–4.5;Ω:rhabdomyolysis workup

Two patients (Cases NO 1,and 9) were also hypotensive and were in septic shock, so they were hydrated 20 cc per kilogram, and inotrope (norepinephrine infusion;in case NO. 9 vasopressin was also started) in addition to the broad-spectrum antibiotic were started; patient NO. 1 also

presented with refractory hyperthermia with rhabdomyolysis ,and malignant hyperthermia (MH)-like syndromes. AKI was found in 4 patients. All of our patients had decreased level of consciousness, and three of them (cases 1,3 and 9) had GCS less than 8, so they were intubated (in both of them, brain CT scan was normal and did not have criteria for brain edema).

Four cases were managed with central venous catheter insertion (cases 1, 3, 6, and 9), with the catheters placed into the jugular veins. High C-reactive protein values were found in four cases (1, 3, 6, and 9). In our study, all patients survived to hospital discharge, and no permanent neurologic or other sequelae were documented.

Discussion

HHS and mixed DKA-HHS are less frequent than isolated DKA, especially in pediatric patients whose incidence rate is lower, so their diagnosis and treatment are challenging. The frequency of mixed DKA-HHS in our center was about 1.98%. In a study; Schmitt et al. reported 29% in pediatric patients with type 2 of DM(3) ; Agrawal et al. and Francisco et al. showed 13.8% and 27% (6).

Of nine patients, five cases were known cases of DM, and in four patients (44.4%), mixed DKA-HHS was the first presentation sign of DM; the main reason for their disease was delayed diagnosis and treatment. A study in Australia showed that DKA was the first presentation of the majority of their patients (48%) (8);in another study by Oyarzabal Irigoyen et al., it was 39.5% (9); moreover, in a study conducted in Italy, DKA was found in 38.5%, but severe DKA was seen in 10.3% of patients as the first presenting sign of DM (10).

Of five patients who had diabetes and had already received insulin, three patients had poor metabolic control, and one patient (case NO. 1) had stopped taking insulin due to fever and lethargy.

The main goals for DKA treatment are fluid replacement, correction of acidosis, gradual correction of hyperglycemia and hyperosmolarity, prevention and treatment of DKA complications, and its treatment(1). Assessment of the degree of dehydration depends on physicians and varies among the examiners, and it mainly depends on physical exam; skin turgor, mucosal dryness, weak pulse, and hypotension (1), but it seems not to be effective in the obese patients.In DKA, fluid therapy is a double-edged sword; its primary role is to provide an adequate circulatory volume, but we should consider that overhydration would increase the risk of brain edema(1). According to DKA severity, fluid replacement therapy usually is achieved over 48 hours and calculated by calculating maintenance and volume deficit. Volume deficit is usually considered 10 percent in severe DKA; however, more fluid loss and dehydration should be considered in DKA-HHS cases, and delay in diagnosis might result in more complications and worse outcomes(1, 11, 12). Mixed DKA-HHS cases should be monitored regularly for overhydration and any evidence of cerebral edema; we monitor our patients with clinical signs of adequate blood flow in addition to laboratory data(blood glucose,and serum osmolality), so we increased the percent of fluid deficit up to16% in some patients.

In DKA-HHS, as these patients had significant ketoacidosis, insulin was initiated according to DKA principles after initial fluid resuscitation; however, the rate of glucose and effective osmolality decline was monitored closely because of the concomitant hyperosmolar state.,and it is unlike HHS that we defer insulin infusion till the time which serum glucose is no longer decreasing at least 50 mg/dL,in DKA we should be aware of decreasing serum glucose that shuld be less than 90 mg/dLper hour;but in HHS it is less(~ 50–75 mg/dL) per hour;serum osmolality is the other point of concern that should not decrease more than 3 mosmol/kg/hr (that is mainly considered in HHS treatment) [1];in our patients we considered to decreasing serum glucose less than 75 mg/dL,and serum osmolality less than 3 mosmol/kg/hr.

The malignant-hyperthermia-like syndrome associated with rhabdomyolysis is a rare, life-threatening complication of DKA whose etiology is not clear (13, 14); it occurred in one of our patients (case NO.1) that presented on the 2nd day of admission, and insulin infusion with refractory hyperthermia increased the level of creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and rhabdomyolysis; the etiology was probably an infection.

There is contemporary pediatric evidence supporting a strong association between hyperosmolar presentations and AKI;. AKI occurred in 44.4% of our patients. This is broadly consistent with previous pediatric hyperosmolar DKA cohorts, although reported rates vary according to diagnostic criteria and the population studied (3, 15, 16).The combination of severe dehydration, hyperosmolality, and impaired renal perfusion likely contributes to this increased risk. These findings support close monitoring of renal function and urine output during initial fluid management.

Interestingly, all nine patients in our cohort were female. Given the small sample size and single-center design, this finding should be considered hypothesis-generating rather than evidence of a sex-specific predisposition.

The rate of mortality and complication was higher in those presented with HHS or mixed DKA-HHS(2), but fortunately, there was no mortality among our patients.

Infection is one of the main predisposing factors for DKA and HHS; four cases of our patients had increased CRP levels,and two patients presented with septic shock. The possible etiologies for decreased level of consciousness in DKA, HHS others than cerebral edema are low PH and hyperosmolality(17); in our study, all the patients presented with altered mental status, and GCS in three patients was less than 8, but their brain CT scan was normal.

The major limitation of this study was the low number of patients related to a lower incidence of mixed DKA-HHS.

Conclusion

Mixed DKA-HHS requires modification of standard DKA management because of the additional risks associated with severe hyperosmolality and dehydration. Therefore, early recognition is crucial for appropriate management, identification and treatment of precipitating factors, and prevention of complications. Pediatricians should be aware of the clinical characteristics and diagnostic criteria of this condition. However, further investigations are needed to accurately determine the degree of fluid deficit in children with mixed DKA-HHS and to establish the optimal strategy for fluid-deficit estimation.

Abbreviations

Diabetic ketoacidosis (DKA); diabetes mellitus (DM); Hyperglycemic hyperosmolar state (HHS); pediatric intensive care unit (PICU)

Declarations

Acknowledgments:

The authors would like to thank Shiraz University of Medical Sciences, Shiraz, Iran, and Center for Development of Clinical Research of Namazi Hospital and Dr. Nasrin Shokrpour for editorial assistance and PICU nurses in Namazi Hospital who involved in caring for this patient.

Financial Supporting:

The authors have not declared a specific grant for this research from any funding agency in public, commercial or not-for-profit sectors

Conflict of Interest Statement: none

Ethics approval and consent to participate:

This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (approval ID: IR.SUMS.MED.REC.1398.134). Written informed consent was obtained from the patients' parents and submitted to the ethics committee.

Authors' contributions:

AS planned the study and wrote the manuscript, AN gathered patients' data. FsM was a scientific consultant and edited the manuscript and submitted the manuscript. All authors discussed the results and contributed to the final manuscript.

References

1. Wolfsdorf JI, Glaser N, Agus M, Fritsch M, Hanas R, Rewers A, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state. Pediatr Diabetes. 2018;19:155–77.
2. Pasquel FJ, Tsegka K, Wang H, Cardona S, Galindo RJ, Fayfman M, et al. Clinical outcomes in patients with isolated or combined diabetic ketoacidosis and hyperosmolar hyperglycemic state: a retrospective, hospital-based cohort study. Diabetes Care. 2020;43(2):349–57.
3. Schmitt J, Rahman AF, Ashraf A, Endocrinology. Diabetes Metab. 2020;3(3):e00160.
4. Rosilio M, Cotton JB, Wieliczko MC, Gendrault B, Carel JC, Couvaras O, et al. Factors associated with glycemic control. A cross-sectional nationwide study in 2,579 French children with type 1 diabetes. The French Pediatric Diabetes Group. Diabetes Care. 1998;21(7):1146–53.
5. Elamin A, Altahir H, Ismail B, Tuvemo T. Clinical pattern of childhood type 1 (insulin-dependent) diabetes mellitus in the Sudan. Diabetologia. 1992;35(7):645–8.
6. Agrawal S, Baird GL, Quintos JB, Reinert SE, Gopalakrishnan G, Boney CM, et al. Pediatric diabetic ketoacidosis with hyperosmolarity: clinical characteristics and outcomes. Endocr Pract. 2018;24(8):726–32.
7. Workgroup K. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2(1):1–138.
8. Patwardhan R, Gorton S, Vangaveti VN, Yates J. Diabetic ketoacidosis incidence in children at first presentation of type 1 diabetes at an Australian regional hospital: The effect of health professional education. Pediatr Diabetes. 2018;19(5):993–9.
9. Irigoyen MO, Cuartero BG, Castellanos RB, Lacruz MT, Gila AG, Casado IG, et al. Ketoacidosis at onset of type 1 diabetes mellitus in pediatric age in Spain and review of the literature. Pediatr Endocrinol reviews: PER. 2012;9(3):669–71.
10. Zucchini S, Scaramuzza AE, Bonfanti R, Buono P, Cardella F, Cauvin V et al. A multicenter retrospective survey regarding diabetic ketoacidosis management in Italian children with type 1 diabetes. Journal of diabetes research. 2016;2016.
11. Zeitler P, Haqq A, Rosenbloom A, Glaser N. Hyperglycemic hyperosmolar syndrome in children: pathophysiological considerations and suggested guidelines for treatment. J Pediatr. 2011;158(1):9–14. e2.

12. Nambam B, Menefee E, Gungor N, Mcvie R. Severe complications after initial management of hyperglycemic hyperosmolar syndrome and diabetic ketoacidosis with a standard diabetic ketoacidosis protocol. J Pediatr Endocrinol Metab. 2017;30(11):1141–5.
13. Price A, Losek J, Jackson B. Hyperglycaemic hyperosmolar syndrome in children: patient characteristics, diagnostic delays and associated complications. J Paediatr Child Health. 2016;52(1):80–4.
14. Hollander AS, Olney RC, Blackett PR, Marshall BA. Fatal malignant hyperthermia-like syndrome with rhabdomyolysis complicating the presentation of diabetes mellitus in adolescent males. Pediatrics. 2003;111(6):1447–52.
15. Orban J-C, Maizière E-M, Ghaddab A, Van Obberghen E, Ichai C. Incidence and characteristics of acute kidney injury in severe diabetic ketoacidosis. PLoS ONE. 2014;9(10):e110925.
16. Myers SR, Glaser NS, Trainor JL, Nigrovic LE, Garro A, Tzimenatos L, et al. 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–e.
17. Nyenwe EA, Razavi LN, Kitabchi AE, Khan AN, Wan JY. Acidosis: the prime determinant of depressed sensorium in diabetic ketoacidosis. Diabetes Care. 2010;33(8):1837–9.