

# Incidence, predisposing factors and complications of Diabetic Ketoacidosis in diabetic patients

## Original Article

Morteza Alijanpouraghamaleki (MD) <sup>1</sup>

Zohreh Shabanzadeh (MD) <sup>1</sup>

Masoomeh Rezapour (MD) <sup>2</sup>

Ali Bijani (MD) <sup>1</sup>

Faeze Aghajpour (BSc) \*<sup>1</sup>

1. Non-Communicable Pediatric Diseases Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, IR Iran.
2. Babol University of Medical Sciences, Babol, IR Iran.

### \* Correspondence:

Faeze Aghajpour (BSc),

Non-Communicable Pediatric Diseases Research Center, No 19, Amirkola Children's Hospital, Amirkola, Babol, Mazandaran Province, 47317-41151, IR Iran.

**E-mail:** faezeaghaianpour@yahoo.com

**Tel:** +98 1132346963

**Fax:** +98 1132346963

**Received:** 20 June 2016

**Revised:** 16 July 2016

**Accepted:** 11 Aug 2016

### Abstract:

**Background:** Diabetic ketoacidosis (DKA) is the final consequence and life-threatening complication of severe insulin deficiency in type 1 diabetes with occurrence of 20-40%. The aim of this study was to investigate the incidence and predisposing factors of DKA and its consequences.

**Methods:** This retrospective study was performed on 128 diabetic patients in Amirkola Children's Hospital in 2005-2013. Patients' data were recorded in a predetermined questionnaire. The data were analyzed using SPSS.18.

**Results:** Of all 128 hospitalized diabetic patients, 103 patients (80.5%) were referred for the first time and 25 (19.5%) patients were previously treated with insulin. Of total 128 patients, 71 (55.5%) had some degree of ketoacidosis that severe ketoacidosis was the most common form (in 36 cases; 50.7%). Among patients with the diagnosis of ketoacidosis (71 patients), 54 patients (76%) presented with DKA as the first symptom of diabetes. Generally, the predisposing factors of ketoacidosis were seen in 39 (54.9%) patients, which were due to infections and insulin therapy discontinuation in 27 (69.23%) and 12 (30.76%) of them, respectively. In patients with previous diagnosis of diabetes mellitus and history of admission with diabetic ketoacidosis, 70.58% had previous treatment cessation.

**Conclusions:** In the current study, the incidence of ketoacidosis was high (55.5%). This subject seems to be related to lack of information about diabetes mellitus among population who require the universal education. On the other hand, in respect to high incidence of DKA among patients with cessation of previous insulin treatment, rigorous and complete training of them is critical.

**Keywords:** Diabetes Mellitus, Diabetic Ketoacidosis, Child

### Citation:

Alijanpour M, Shabanzadeh Z, Rezapour M, et al. Incidence, predisposing factors and complications of Diabetic Ketoacidosis in diabetic patients. *Caspian J Pediatr* Sep 2016; 2(2): 142-7.

### Introduction:

Diabetes mellitus is a common and chronic metabolic syndrome which its major biochemical aspect is hyperglycemia <sup>[1, 2]</sup> and is divided into two categories -type 1 and 2. Type 1 diabetes caused by the destruction of pancreatic beta cells by different autoantibodies. It is also determined by the low production of insulin or its absence in the body and it is necessary to inject insulin for preventing the serious complications such as diabetic ketoacidosis <sup>[1, 3]</sup>. Symptoms such as polyuria, polydipsia, weight loss, nocturia, difficulty in weight gaining, vaginal candidiasis, recurrent skin infections, irritability and dysfunction in homework appear in diabetic children <sup>[1, 4]</sup>. The incidence of type 1 diabetes is rising rapidly in some specific areas. About 40% of patients with this type of diabetes are aged less than 20 years and the highest incidence is belonged to two levels of age- the age of 5-7 years and the maturity age <sup>[1]</sup>. Serious complications such as cerebral edema which is in fact most common cause of death in diabetic ketoacidosis, can occur during the treatment of this disease <sup>[5, 6]</sup>. Radiographic imaging is frequently unhelpful in making the

diagnosis of cerebral edema. Consequently, each patient must be closely monitored, including frequent neurologic checks for any signs of increasing intracranial pressure, such as a change of consciousness, depressed respiration, worsening headache, bradycardia, apnea, pupillary changes, papilledema, posturing, and seizures. [1, 7]

In addition, abnormalities such as hypoglycemia, hyperkalemia, hypokalemia and hyponatremia can arise and it requires tight monitoring during the treatment of diabetic ketoacidosis [8-13].

Mortality rate in diabetic ketoacidosis is 0.15-5% [6, 10]. The most common predisposing factors of diabetic ketoacidosis are infections, cessation of previous insulin therapy and new onset of diabetes [8, 13]. Diabetic ketoacidosis is a life-threatening and medical emergency [6, 8, 10, 13] and it is more common in younger than in adult [13] and the lack of early treatment is accompanied by high mortality [8].

Since diabetes is the most common endocrine disorder and the ketoacidosis is considered as a medical emergency, we decided to investigate the frequency of symptoms, clinical signs, predisposing factors and its complications during the years of 2005-2013 in Amirkola Children's Hospital.

## Methods:

This cross-sectional study was conducted on 128 diabetic patients referred to Amirkola Children's Hospital during 2005-2013. Data about current patients were obtained in admission time at the emergency room and pediatric ICU ward. In new cases, the blood sugar of children hospitalized with polydipsia, polyuria, and weight loss signs, were checked using the Glucooxide method from Pars Azmoon (Iran) kit and diabetes was diagnosed according to diabetic diagnosis criteria (table 1) [1], then a careful study of the arterial blood gas (ABG) was performed whether the patient had the diabetic ketoacidosis or not (table 2) [1].

During hospitalization, the patients were evaluated in terms of the probable risk of various infections, electrolytes (sodium, potassium, glucose) and consciousness. Sodium and potassium, venous blood glucose and capillary blood glucose were determined by Ion Selective Electrode (ISE) device, Glucooxide method from Pars Azmoon (Iran) kit and glucometer ACCU-CHEK (Roche Company in Germany), respectively.

The study was approved by the local Ethics Committee of Babol University of Medical Sciences

and all obtained information was recorded in the questionnaire. The data were then analyzed using SPSS18, Chi-Square test and T-test (P-value <0.001 was significant).

## Results:

Totally, 128 patients were surveyed in the present study. The incidence of ketoacidosis was high (55.5%). Seventy (54.7%) of them were male and 58 (45.3%) were females, respectively. The mean age of the children was  $8.57 \pm 3.27$  years with a median of 9 years. There was no significant difference in the admission time in various months of year.

Most cases (35 persons) were referred to hospital in summer while the least cases were visited in autumn (28), respectively.

The average time from onset of symptoms to the admission time was  $14.5 \pm 17.7$  days with a median of 7 days. In a Total, 103 patients (80.5%) were referred to the center for the first time and they had no history of previous diabetes but 25 patients (19.5%) were previously treated with insulin and 8 (6.25%) cases had a positive familial history.

The most common symptoms of patients were polyuria and polydipsia in 111 individuals (86.7%) at the first time of their admission. Weight loss, nausea and vomiting, nocturia and abdominal pain were observed in 77 (60.20%), 39 (30.9%), 17 (13.30%) and 34 (26.6%) patients, respectively.

Seventy-one (55.5%) of the patients had some degree of ketoacidosis that in terms of severity, the severe ketoacidosis with frequency of 50.7% (in 36 cases) was more common than others. After that, mild and moderate ketoacidosis were 14 (19.7%) and 21 patients (29.6%), respectively.

Fifty four patients (76%) of total 71 patients had diabetic ketoacidosis as a first presenting sign. The relationship between the symptoms (each of them) of immediate admission was compared to the severity of ketoacidosis. Only nausea and vomiting were significant with  $p\text{-value} < 0.001$  that represented the severity of ketoacidosis. In addition, there was no relationship between other symptoms and the severity of ketoacidosis. Thirty-four (47.88%) of 71 patients with ketoacidosis had nausea and vomiting.

Generally, the predisposing factors of ketoacidosis were seen in 39 (54.9%) patients, which were due to infections and insulin therapy discontinuation in 27 (69.23%) and 12 (30.76%) of them, respectively (Table 3). There was no relationship between the severity of

ketoacidosis and infection as predisposing factors of ketoacidosis (p-value>0.001).

Another predisposing factor of diabetic ketoacidosis was discontinuing of previous insulin therapy including the treatment stop arbitrarily, cessation of doing the doctor's order, lack of access to drugs and insufficient awareness of the disease. Twelve patients (17%) of 71 had cessation of previous treatment as a predisposing factor of ketoacidosis, that 9 (12.67%) and 3 (4.33%) of them had arbitrary cutoff and lack of information, respectively. On the other hand, doctor prescription and lack of access to medicines weren't seen in these patients.

In this study, 25 patients had a prior history of diabetes that 17 patients were admitted with ketoacidosis and 12 of 17 patients (52.9%) had history of Insulin therapy discontinuation (Table 3). Moreover, 32 cases (45.07%) of 71 patients did not have any risk factors according to our investigation. In terms of

complications during treatment, hypokalemia, hyperkalemia, hyponatremia and hypernatremia were observed in 15 (21.12%), 11 (15.49%), 20 (28.16%) and 8 (11.26%) patients, respectively.

In the present study, 25% and 27.8% of individuals with severe ketoacidosis suffered from hypokalemia and hyponatremia, respectively. The P Value<0.001 was obtained in this study about relationship between the severity of ketoacidosis and the abnormalities of potassium and sodium, which indicated the direct relationship between these two items and the greater severity of ketoacidosis causes the more electrolyte abnormalities. There was no relationship between the severity of diabetic ketoacidosis and glucose abnormalities (P Value>0.001).

None of the patients experienced cerebral edema during the time of hospitalization. All of patients were discharged from the hospital with general good condition and the mortality rate was zero.

**Table 1. Diagnostic Criteria for Impaired Glucose Tolerance and Diabetes Mellitus**

Impaired Glucose Tolerance	Diabetes Mellitus
Fasting glucose 100-125 mg/ dL (5.6-7.0 mmol/L) 2-hr plasma glucose during the OGTT ≥140 mg/dL, but <200 mg/dL (11.1 mmol/L)	Symptoms* of diabetes mellitus plus random or casual plasma glucose ≥200 mg/dL (11.1 mmol/L) or Fasting (at least 8 hr) plasma glucose ≥126 mg/dL (7.0 mmol/L) or 2 hr plasma glucose during the OGTT ≥200 mg/dL or Hemoglobin A1C ≥6.5%**

\* Symptoms include polyuria, polydipsia, and unexplained weight loss with glucosuria and ketonuria.

\*\* Results should be confirmed by repeat testing if in absence of unequivocal hyperglycemia, OGTT, oral glucose tolerance test.

**Table 2: Classification of Diabetic Ketoacidosis**

	Normal	Mild	Moderate	Severe
CO <sub>2</sub> (mEq/L, Venous)*	20- 28	16- 20	10- 15	< 10
pH (Venous)*	7.35- 7.45	7.25- 7.35	7.15- 7.25	< 7.15
Clinical	No Change	Oriented, alert but fatigued	Kussmaul respirations, oriented but sleepy; arousable	Kussmaul or depressed respirations; sleepy to depressed sensorium to coma

\*CO<sub>2</sub> and pH measurements are dependent on method; normal ranges may vary.

Severe Hyponatremia (corrected Na> 150 mEq/L) would also be classified as severe diabetic ketoacidosis.

**Table 3. Frequency of predisposing factors of ketoacidosis**

Predisposing Factor	N (%)	Total N (%)
Respiratory	17 (24.30)	27 (69.23)
Gastrointestinal	3 (4.30)	
Urinary tract	2 (2.80)	
Hepatitis	1 (1.40)	
Otitis	1 (1.40)	
Chickenpox	1 (1.40)	
Orchitis	1 (1.40)	
Mucormycosis	1 (1.40)	
Cessation of treatment	Arbitrary cutoff 9 (12.67)	12 (30.76)
Lack of information	3 (4.33)	
Total		39 (54.9)

## Discussion:

According to this study, frequency of ketoacidosis among our hospitalized patients with diabetes mellitus was 55.5%. This frequency was 42% in the study of W.Jackson et al.'s [17]. Sharifi et al.'s studied on 114 diabetic patients. They concluded that 37.5% had diabetic ketoacidosis among those who suffered from acute complications [12]. Maniatis et al.'s conducted a study on 383 patients in America and 28.4% of them suffered from diabetic ketoacidosis [26]. Our results were relatively higher than other reports that maybe due to lack of information on diabetes mellitus between families and general population and medical community.

Diabetic ketoacidosis was the first symptom of diabetes in 76% of our patients. The frequency was 65.9% in the study of Demirbilek et al.'s [29]. In a study performed by Moayeri et al.'s 37.3% cases of 83 patients had diabetic ketoacidosis as the first manifestation of diabetes [11].

In the present study, the time from the onset of symptoms to hospital admission was  $14.5 \pm 17.7$  days (minimum 1 day, maximum 90 days) but it was lower ( $9.4 \pm 9.5$ ) in the study of Shiva et al.'s [19].

In this study, 50.7% of all cases with DKA had severe ketoacidosis in Razavi's study on 200 patients, 54.5% of patients had severe ketoacidosis, too [16]. As observed, the most common symptoms were polyuria and polydipsia (together) with 86.7% in the present study while the most common symptoms were polyuria (66%) and nausea and vomiting (64%) in Rafiee's study [9].

In a study of Razavi, the prevalence of polydipsia, polyuria, weakness and abdominal pain was 85.4%, 83.3%, 68.8% and 52.1%, respectively [16]. The frequency of nausea and vomiting in patients with ketoacidosis was 47.88% in the current study but it was 33.3% in the study of Razavi [16]. Generally, the predisposing factors of ketoacidosis were seen in 39 (54.9%) patients, which were due to infections and insulin therapy discontinuation in 27 (69.23%) and 12 (30.76%) of them, respectively. Moreover, Sheykhoul Eslami et al.'s stated that 40% of patients had infections and the most common of them was urinary tract infection with 54% [10].

Another predisposing factor of ketoacidosis in our study was discontinuation of treatment in diabetic patients treated with insulin that 70.58% of them had previous treatment cessation, while Rezvanfar et al.'s studied on 30 patients 50% of patients had discontinued insulin [8]. Mashayekhi et al.'s performed

a study on 50 patients over 5 years and 52% of patients had discontinued treatment in their study [23]. Rafiee was performed the study on 33 patients and he expressed that the cause of repeated ketoacidosis in 75% of cases was due to the lack of access to syringes and insulin [9].

In the present study, there was no specific cause for developing ketoacidosis (infection or cessation of treatment) in 45.07% of the patients, but this rate was 12% in the study of Bakhsaayesh et al.'s. [18].

In terms of the complications during the treatment, hypokalemia, hyperkalemia, hyponatremia and hypernatremia were observed in 15 (21.12%), 11 (15.49%), 20 (28.16%) and 8 (11.26%) patients, respectively and in a study by Mashayekhi et al.'s hypokalemia, hyperkalemia and hypoglycemia were observed in 24%, 22% and 8% of patients, respectively [23].

Cerebral edema is a serious and life-threatening complication of diabetes but none of our patients experienced which is similar to the result of Muir et al.'s [11]. The mortality rate in the current study was zero while it was one in the study of Nakhjavani et al.'s on 45 patients with diabetes mellitus in this center owing of DKA; however, Sharifi reported the mortality rate was 11.1% in his study [12].

By considering a common pattern of ketoacidosis in hospitalized patients in this study in comparison with other studies, it seems that the lack of information on diabetes mellitus in children among general population and medical community is an important factor so better training is necessary for all health care workers and also the community.

In addition, due to the significant statistics of ketoacidosis in patients with a diagnosis of diabetes, it needs more training on the continuous proper treatment of diabetes and further medical care.

## Acknowledgment:

We are grateful to the Clinical Research Development Committee of Amirkola Children's Hospital, Non-Communicable Pediatric Diseases Research Center of Babol University of Medical Sciences, Health Research Institute and all children and parents for their contribution to this study.

**Funding:** This study was supported by a research grant and General Physician thesis of Dr Zohreh Shabanzadeh from the Non-Communicable Pediatric

Diseases Research Center of Babol University of Medical Sciences (Grant Number: 9132818).

**Conflict of interest:** The authors declare that they have no competing interests.

## References:

1. Kliegman RM, Behrman RE, Jenson HB, Stanton BM. Nelson textbook of pediatrics: 18th edition, Philadelphia, Elsevier Health Sciences; 2007: 185, 215, 517, 2404, 2405, 2412, 2763, 2775.
2. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2010; 33(Supplement 1): S62-9.
3. American DA. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2006 01; 29(1): S43-8.
4. Henry M, Kronenberg SM, Kenneth S, Polonsky P. Reed Larsen. Williams Textbook of Endocrinology, 11th edition Philadelphia, USA: Saunders Elsevier. 2008: 1407.
5. Sperling M, Weinzimmer S, Tamborlane W. Sperling Pediatric Endocrinology. 3th edition Philadelphia: Saunders Company; 2008: 392
6. Brook CG, Clayton P, Brown R. Brook's clinical pediatric endocrinology: 6th edition, John Wiley & Sons; 2009: 392, 459, 468.
7. Marcin JP, Glaser N, Barnett P, et al. Factors associated with adverse outcomes in children with diabetic ketoacidosis-related cerebral edema. J Pediatr 2002; 141(6): 793-7.
8. Rezvan Far MR, Gafari A. Assesment of Clinical Signs, Labratory Findings and Predisposing Factors in Diabetic Ketoacidosis Patients in Arak Vali Asr Hospital. Arak Med Uni Journal 2002; 4(4 (17)): 32-6. [Text in Persian]
9. Rafii M. A Study of the Clinical Manifestations, Biochemical Findings, Precipitating Factors and Complications in 56 Episodes of Diabetic Ketoacidosis. Iran J Public Health 1998; 27 (1-2): 71-80. [Text in Persian]
10. Sheikholeslami H, Ziaee A, Shariatmadari M. Evaluation of clinical manifestation, laboratory data and precipitating factors in patients with Diabetic ketoacidosis in educational and medical care center of Boooli Sina in Ghazvin (1999-2004). Birjand Uni Med Sci 2008; 15(2): 60-65. [Text in Persian]
11. Moayeri H, Mostafavi F, Golabi Dezfuli P. The Changes of Serum Sodium, Potassium, Glucose and Blood Gases during the First Eight Hours of Treatment in Diabetic ketoacidosis. Iran J Endocrin Metabolism 2004; 6(2): 123-31. [Text in Persian]
12. Sharifi H, Afshar M, Akbari H, Matini S. Acute complications of diabetes mellitus in patients hospitalized in Shahid Beheshti Hospital, Kashan, 1991-99. Kashan Uni Med Sci J (FEYZ) 2002; 6 (1): 56-60. [Text in Persian]
13. Trachtenbry DE. Diabetic ketoacidosis. American Academy of family physicians j 2005; 71(9): 1705-14.
14. Satlin LM. Potassium. Avner ED, Harmon WE, Niaudet P, Yoshikawa N. Pediatric Nephrology: Springer Berlin Heidelberg, 6th edition; 2009: 185-204.
15. Nakhjavani N, Rahimi Gh. Evaluation of epidemiologic and clinical manifestation of Children with type 1 diabetes in patients admitted to Amirkola Children's Hospital. Babol Uni Med Sci 2003; Tez Number: 745.
16. Razavi Z. Frequency of ketoacidosis in newly diagnosed type 1 diabetic children. Oman Med J 2010; 25(2): 114-7.
17. Jackson W, Hofman PL, Robinson EM, et al. The changing presentation of children with newly diagnosed type 1 diabetes mellitus. Pediatr Diabetes 2001; 2(4): 154-9.
18. Bakhshayeshkaram M, Dabbaghmanesh AR, Dabbaghmanesh MH, Ranjbar Omrani GH. Precipitating Factors, Biological Characteristics and Clinical Manifestations in Patients Admitted With Diabetic Ketoacidosis in Shiraz Nemazee Hospital. Iran J Endocrinology and Metabolism 2013; 14(6): 531-7. [Text in Persian]
19. Shiva S, Zarrintan A. Study of Clinical, Laboratory & Epidemiologic Characteristics of Diabetic Ketoacidosis in Tabriz Children's Hospital during 2001-2007. Med J Tabriz Uni Med Sci&Health Services 2010; 32(5): 53-7. [Text in Persian]
20. Rosenbloom AL. The management of diabetic ketoacidosis in children. Diabetes Ther 2010; 1(2): 103-20.
21. Orłowski JP, Cramer CL, Fiallos MR. Diabetic ketoacidosis in the pediatric ICU. Pediatr Clin North Am 2008; 55(3): 577-87.
22. Kotori VM, Gashi N, Toro H. Severe Ketoacidosis at onset of type 1 diabetes in children due to late diagnosis. Diabetologia Croatica Kosova 2007, 36(3): 59-65.
23. Mashayekhi M, Azimi R, Sadeghian B. Study of Predisposing Factors, Complications and Mortality



- of Diabetic Ketoacidosis in teens and adults. RJMS 2001; 8(23): 63-9. [Text in Persian]
24. Barati M, Ghasemi F, Fathi M. Evaluation of Diabetes Mellitus in Patients with sepsis. RJMS 2007; 13(53): 33-9. [Text in Persian]
25. Skinner TC. Recurrent diabetic ketoacidosis: causes, prevention and management. Horm Res 2002; 57 (Suppl 1): 78-80.
26. Maniatis AK, Goehrig SH, Gao D, et al. Increased incidence and severity of diabetic ketoacidosis among uninsured children with newly diagnosed type 1 diabetes mellitus. Pediatr Diabetes 2005; 6(2): 79-83.
27. Lin SF, Lin JD, Huang YY. Diabetic ketoacidosis: comparisons of patient characteristics, clinical presentations and outcomes today and 20 years ago. Chang Gung Med J 2005; 28(1): 24-30.
28. Levin DL. Cerebral edema in diabetic ketoacidosis. Pediatric Critical Care Medicine 2008; 9(3).
29. Demirbilek H, Ozbek MN, Baran RT. Incidence of type 1 diabetes mellitus in Turkish children from the southeastern region of the country: a regional report. J Clin Res Pediatr Endocrinol 2013; 5(2): 98-103.