Clinical and Biochemical Characteristics of Diabetes Ketoacidosis in a Tertiary Hospital in Riyadh

Mussa H. Almalki1,2, Baduruden Mahmood Buhary1, Shawana Abdulhamid Khan1, Abdurahman Almghamshi1 and Fahad Alshahrani3

1Obesity, Endocrine and Metabolism Centre, King Fahad Medical City (KFMC), Riyadh, Saudi Arabia. 2King Fahad Medical City, College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia. 3King Abdulaziz Medical City, College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia.

ABSTRACT: Diabetes is the fifth leading cause of death worldwide. Diabetic ketoacidosis (DKA) is a life-threatening acute complication of diabetes. The aim of this study is to investigate the clinical and biochemical characteristics of DKA among 400 patients admitted to hospital, most of whom had type 1 diabetes (n = 372; 93%). Vomiting (n = 319; 79.8%), nausea (n = 282; 70.5%), and abdominal pain (n = 303; 75.8%) were the presenting symptoms most commonly experienced by the patients. Tachycardia was the most common clinical sign noted in the patients on admission (n = 243; 61.8%). The predominant precipitating cause of DKA was noncompliance to an insulin regimen (n = 215; 54.2%). Recurrent DKA admissions in type 1 diabetes patients was higher than those with type 2 diabetes (n = 232 versus n = 9, respectively; P = 0.002). Recurrent DKA admissions in female patients were higher than in male patients (n = 167 versus n = 74, respectively; P = 0.002). Continued diabetic education (given to n = 384; 94%) and counseling on the importance of adhering to the recommended medical regime, addressing the social and cultural barriers that precipitate DKA, as well as the provision of timely medical attention may greatly reduce DKA episodes and their associated complications.

KEYWORDS: diabetes, diabetic ketoacidosis, presenting symptoms, precipitating cause

Introduction

Diabetes is considered the fifth leading cause of death, and it is a leading cause of morbidity and mortality in the developed world, as well as in many developing countries. Diabetes prevalence (in adults) is reported to be 24% in Saudi Arabia,1 which is higher than that reported in the developed countries. According to the International Diabetes Federation, the diabetes rate in Saudi Arabia in 2015 was 17.6%.2

Diabetic ketoacidosis (DKA) is one of the life-threatening acute complications of diabetes mellitus (DM) that mainly occurs in type 1 diabetes patients, as well as in some patients with type 2 diabetes. It tends to present under stressful conditions or in association with illnesses that feature metabolic decompensation. DKA is characterized by hyperglycemia, ketoacidosis, and ketonuria.3 DKA affects both children and adults and requires immediate attention. The true annual incidence rate for DKA is difficult to establish, but population-based studies have reported ranges from 4.6 to 8 cases per 1,000 patients with diabetes.4,5 DKA rates may be between 5% and 7% in individuals aged <18 years.6 The global incidence of DKA is influenced by various factors and is reflective of the prevalence of diabetes in that population.7,8

Mortality due to DKA is <5% according to the American Diabetes Association (ADA).8,9 Most cases of DKA arise due to missed insulin doses, either as a result of negligence or poor socioeconomic status.10 Other precipitators of DKA include infections, cerebrovascular accidents, alcohol/drug abuse, pancreatitis, myocardial infarction, and trauma. Simple lifestyle modifications, such as educating the patients about not missing any insulin doses—especially during illness—and providing the patients with an adequate insulin regimen, can greatly reduce DKA occurrence.

The mortality rate associated with DKA depends on the experience of the treating hospital in dealing with this condition;11 thus, it is critical that patients detect DKA and get medical help as soon as possible. The management of DKA has improved over the years, as evident by the decrease in the death rate.12 It is recommended that ketoacidosis should be considered upon the first admission of diabetic children and high-risk patients; in this vein, blood glucose and ketones should be measured upon first admission to the emergency room. Despite the major health burden of DKA, there have been a few studies conducted on its clinical and biochemical characteristics in the Kingdom of Saudi Arabia (KSA) or the Arab world.

Diabetic education and the importance of correct medication should be taught from the beginning of diabetes.
diagnosis, especially for type 1 diabetes patients, in order to identify DKA symptoms at the earliest possible time. Accordingly, we propose to perform a retrospective cohort study of the clinical and biochemical characteristics of DKA in diabetic patients presenting to a tertiary center in Riyadh, KSA. These risk factors will be analyzed by studying their association with DKA. This study will define and determine the clinical and biochemical characteristics of DKA. Our study will provide the critical information required for the KSA; it will allow the appropriate measures to be implemented to optimally address the prevention, diagnosis, and treatment of DKA; and it will also provide intensive education to increase the awareness of DKA, DM, and other risk factors.

Methods
This study is a retrospective observational cohort study of 400 consecutive patients with DKA who presented to the emergency room at the tertiary center from June 2014 to May 2015. This research complied with the principles of the Declaration of Helsinki. The sample size is calculated to be 400 patients (154 male and 246 female) at the level of significance of α = 0.05, with an estimated prevalence rate of 30% and 50% for male and female diabetic patients, respectively, with a power of 94%. The large sample size of consecutive cases provides the necessary power to perform a detailed analysis in order to study DKA. Patients under 12 years of age are seen by pediatric endocrinologists; as such, all type 1 and type 2 diabetes patients aged 12 years and older with DKA are included. Cases of DKA will be identified by the ADA (2006) criteria for the definition of DKA; metabolic acidosis is often the most prevalent finding, while the serum glucose concentration is generally below 900 mg/dL (44 mmol/L). However, serum glucose concentrations may exceed 900 mg/dL (50 mmol/L) in comatose patients with DKA. We review all the cases and classify them according to these criteria, with the previously demonstrated validity for enrollment in this retrospective cohort study. Patients with hyperosmolar state and hyperglycemia without ketacidosis were excluded. The availability of clinical data regarding DKA characteristics, glycemic data, the presence of other comorbidities, and documented HbA1c levels were also prerequisites for inclusion in this study.

For each patient, case report forms were completed, and the following variables were collected and recorded in an Excel sheet: age, sex, type and duration of diabetes, missed insulin doses, presenting signs and symptoms, vitals, body mass index, comorbidities, complications, duration of hospital stay, altered consciousness, and mental obtundation. The following investigations were also performed, including electrolyte changes, such as plasma glucose (mg/dL), arterial pH, serum bicarbonate (mEq/L), urine ketones, serum ketones, effective serum osmolality (mOsm/kg), anion gap, HbA1c results, vitamin D, thyroid-stimulating hormone (TSH), FT4, calcium, creatinine, sodium, potassium, and lactate. Definitions were established for all variables to ensure the standardization of data collection. Continuous variables are represented as mean ± standard deviation (SD) and percentages. Unpaired t-tests were used to analyze the differences between means. The data were analyzed using the multivariate logistic regression model. The significance level for the results was set at P < 0.05. The data were analyzed using the Statistical Package for the Social Sciences for Windows version 12. The institutional review board of King Fahad Medical City, Riyadh approved this study.

Results
This study included 400 DKA admissions with a mean ± SD age of 21.4 ± 10.1 years. The overall mean duration of diabetes was 7.6 ± 5.3 years. The admissions included 154 (38.5%) male and 246 (61.5%) female patients. Of the 400 admissions, most (n = 395; 98.8%) of them were Saudis with type 1 diabetes (n = 372; 93%). A previous history of DKA was recorded in 241 (65%) patients, including both type 1 and type 2 diabetes patients. Intensive care unit (ICU) admission was required in 77 (19.3%) patients. The factors that warranted ICU admission were severe DKA as per ADA criteria and classification of DKA. The mean HbA1c level was 11.9% ± 2.6%. The patients’ other baseline characteristics are listed in Table 1.

Table 1. Patient characteristics on admission.

| BASELINE FEATURES | MEAN ± SD |
|-------------------|-----------|
| Age (years)       | 21.4±10.1 |
| Duration of diabetes (years) | 7.6±5.3 |
| HbA1c (%)         | 11.9±2.6  |
| BMI (kg/m²)       | 23±6.1    |
| Hospital stay (days) | 4.6±3.3 |
| Total number of patients | 400 |
| Sex               |            |
| Female            | 246 (61.5) |
| Male              | 154 (38.5) |
| Nationality       |            |
| Non-Saudi         | 5 (1.3)    |
| Saudi             | 395 (98.8) |
| Type of DM        |            |
| Type 1            | 372 (93.0) |
| Type 2            | 28 (7.0)   |
| Previous admissions with DKA | 241 (65.0) |
| ICU admissions     | 77 (19.3)  |
| Family history of diabetes | 162 (40.5) |

| TYPE OF INSULIN | n (%) |
|-----------------|-------|
| Lantus          | 272 (68.0) |
| NPH             | 85 (21.3) |
| Detemir         | 1 (0.3)   |
| Novo rapid      | 266 (66.5) |
| Regular         | 94 (23.5) |
| Novo mix        | 27 (6.8)  |
| Mixtard         | 15 (3.8)  |

Abbreviations: HbA1c, Glycated hemoglobin; BMI, Body Mass Index; DM, Diabetes Mellitus; DKA, Diabetic ketoacidosis, ICU, Intensive Care Unit; NPH, Neutral Protamine Hagedorn.
As documented in the patients’ case report forms, of the 400 admissions, most had vomiting ($n = 319; 79.8\%$), nausea ($n = 282; 70.5\%$), and abdominal pain ($n = 303; 75.8\%$) as the presenting symptoms. Other symptoms included polyuria ($n = 105; 26.3\%$), polydipsia ($n = 113; 28.2\%$), impaired level of consciousness ($n = 83; 20.8\%$), shortness of breath ($n = 55; 13.8\%$), and fever ($n = 56; 14.1\%$). The presenting symptoms are listed in Table 2. The predominant precipitating cause of DKA was noncompliance to the insulin regimen ($n = 215; 54.2\%$). Stress accounted for precipitating DKA in 42 (10.6\%) cases. Symptoms and signs of a triggering illness were pursued with appropriate studies (eg, cultures, imaging studies). Adults had an electrocardiogram to screen for acute MI. Younger patients had stress due to examination and social factors. This was assessed through general history taking. Other factors are presented in Table 3.

Tachycardia was the most common clinical sign noted among the patients on admission ($n = 243; 61.8\%$). Five patients had hypotension. One intrauterine fetal death (suspected due to no fetal movement and confirmed through ultrasound) occurred due to DKA complications in one patient. Bicarbonate treatment was administered to 18 patients (4.5\%), while diabetic education was given to most patients ($n = 384; 94\%$). Table 4 presents the average laboratory results of the patients’ blood tests (pH, blood glucose, HCO$_3$-, anion gap, HbA1c, TSH, FT4, and vitamin D).

The mean ± SD recurrence rate of DKA (number of DKA admissions) was 1 ± 8. Recurrent DKA admissions in type 1 diabetes patients were higher than in type 2 diabetes patients ($n = 232$ versus $n = 9$, respectively; $P = 0.002$). There were more female patients than male patients who required recurrent DKA admissions ($n = 167$ versus $n = 74$, respectively; $P = 0.002$).

### Discussion

A study conducted in Riyadh over the course of 20 years found that 80.4\% of DKA episodes occurred in intermediate, secondary school, and university-level students.$^{13}$ A total of 16.6\% patients with no history of diabetes presented with DKA as the first diabetes-related episode. The study found that precipitating factors for DKA included missed insulin dose in 51.2\% of patients and infections in 22.5\% of patients.$^{13}$ The mean duration of hospital stay was 6.56 ± 3.4 days, and there were no DKA-related deaths reported.

Another study from Jeddah found that both infection and poor compliance to treatment were the most common precipitating factors for DKA, as these were responsible for 54.4\% and 28\% of cases, respectively. DKA occurrence had a male:female ratio of 1.4:1.$^{10}$ A study from Iran showed a higher prevalence of DKA among girls than boys (53.1\% and 46.9\%, respectively).$^{14}$ Moreover, a recent study conducted on pediatric cases in Riyadh showed that nonadherence to insulin accounted for 79.4\% of DKA admissions.$^{15}$ Female patients accounted for 56% of admissions.

Our study found a similar pattern as those reported in these studies, in that nonadherence/discontinued insulin therapy accounted for 54.2\% of DKA admissions, which has been previously reported from various studies in the KSA$^{10,13,15-17}$ and in the neighboring countries.$^{14,18}$ This is mostly due to socioeconomic reasons, where the patients try to stretch their medicine or they think they do not need it after they return to good health. Similarly, they may alter their medication throughout the course of the illness, or simply, they may not strictly adhere to their medication.
There was a predominance of female cases in our study, which concurs with the findings of previous studies, as well as with universal findings. Females are mostly noncompliant with their treatment due to social, personal, and domestic factors. A lack of knowledge of the importance of their medication is also an important factor. The DKA rates can be greatly reduced by providing good diabetic education on the importance of their insulin dosage; we offered this education to most patients (93%).

With regard to presenting complaints, one study found that most patients had a history of vomiting for a duration of at least one day (74%), and 69% of the patients had abdominal pain. Another study found vomiting to be a complaint in 64.7% of admissions. The 20-year study conducted in Riyadh showed that vomiting occurred in 61.6% of patients, and abdominal pain was present in 56.6% of admissions, polyuria was present in 57% cases, and polydipsia was present in 54.1% of admissions. These findings are in agreement with our results. Gastrointestinal manifestations, including abdominal pain, are common in patients with DKA.

The blood glucose level observed at presentation is close to what was stated by other studies, while blood pH and bicarbonate levels were found to be lower. These characteristics were noted in diabetics with poor overall control of diabetes, as evidenced by the high mean A1c levels, which were primarily due to the fact that most patients were adolescents who were nonadherent to their insulin regime. Moreover, about 19.3% of patients required ICU admission; these findings are in agreement with the values associated with DKA. The use of sugary drinks and chocolates by patients thinking they have hypoglycemia when they wrongly self-interpret their symptoms of nausea, vomiting, and abdominal pain complicates matters. Sick-day management should be taught to all patients; the patient should be advised to never discontinue insulin during their illness and that they should seek medical advice early in the course of their illness instead.

The 20-year study also found a reoccurrence of DKA in 54.5% of cases, while our study yielded a value of 65%. One study that was recently performed in Damascus showed that the recurrence of DKA was found in 75% of females and in 87% of type 1 diabetes cases. Our study reported that there was a recurrence rate of 69.29% in females and 67% in type 1 diabetes patients.

The zero mortality rate is highly outstanding compared with the rates found in other studies conducted in the KSA (values of 2.9%, 4.1%, and 3.5% were reported in three previous studies from the KSA). There was only one intrauterine fetal death arising from DKA complications in one patient in our study. This could be attributed to the immediate medical attention given at the center in diagnosing DKA episodes. Continued diabetic education on the importance of adhering to the prescribed medical regime, addressing the social and cultural barriers that precipitate DKA, and the provision of timely medical attention may greatly reduce DKA episodes.

**Conclusion**

Sick-day management should be taught to all patients; in fact, the patient should be advised to never discontinue insulin during the illness. Rather, he/she should seek medical advice early in the course of the illness. Continued diabetic education and counseling on the importance of adhering to medical regimes, addressing the social and cultural barriers that precipitate DKA, and the provision of timely medical attention can greatly reduce DKA episodes and their associated complications. It is our hope that a major reduction in morbidity and hospitalizations due to DKA can be achieved following our study.

**Acknowledgments**

English language editing of this manuscript was provided by Journal Prep.

**Author Contributions**

Conceived and designed the experiments: MHA, BMB. Analyzed the data: MHA, SAK, BMB. Wrote the first draft of the manuscript: BMB, MHA. Contributed to the writing of the manuscript: BMB, MHA. Agree with manuscript results and conclusions: MHA, BMB, SAK, AA, FA. Jointly developed the structure and arguments for the paper: MHA, BMB, FA, AA. Made critical revisions and approved final version: MHA, BMB, AA. All authors reviewed and approved of the final manuscript.

**REFERENCES**

1. Al-Nozha MM, Al-Maamoq MA, Al-Mazzou YY, et al. Diabetes mellitus in Saudi Arabia. Saudi Med J. 2004;25(11):1603–1610.
2. Available at: http://www.idf.org/membership/mena/saudi-arabia
3. Vanelli M, Chiarelli F. Treatment of diabetic ketoacidosis in children and adolescents. Acta Biomed. 2003;74(2):59–68.
4. Faich GA, Fishbein HA, Ellis SE. The epidemiology of diabetic acidosis: a population-based study. Am J Epidemiol. 1983;117:351–358.
5. Johnson DD, Palumbo PJ, Chu C-P. Diabetic ketoacidosis in a community-based population. Mayo Clin Proc. 1980;55:83–88.
6. Maahi DM, Hermann JM, Holman N, et al. Rates of diabetic ketoacidosis: international comparison with 49,859 pediatric patients with type 1 diabetes from England, Wales, the U.S., Austria, and Germany. Diabetes Care. 2015;38(10): 1876–1882.
7. Centers for Disease Control and Prevention. Age-adjusted hospital discharge rates for diabetic ketoacidosis as first-listed diagnosis per 10,000 population, United States, 1988–2009. Available at: http://www.cdc.gov/diabetes/statistics/dkafirst/fig7.htm. 2013. Accessed September 2, 2013.
8. American Diabetes Association. Hyperglycemic crisis in diabetes. Diabetes Care. 2004;27(suppl 1):S94–S102.
9. Kitzbichl AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2009;32(7):1335–1343.
10. Qri FA. Precipitating factors for diabetic ketoacidosis. Saudi Med J. 2002; 23(2):173–176.
11. Levetan CS, Passaro MD, Jablonski KA, Ratner RE. Effect of physician specialty on outcomes in diabetic ketoacidosis. Diabetes Care. 1999;22(11):1790–1795.
12. Lin SF, Lin JD, Huang YY. Diabetic ketoacidosis: comparisons of patient characteristics, clinical presentations and outcomes today and 20 years ago. Cheng Gong Med J. 2005;28:24–30.
Characteristics of diabetes ketoacidosis

13. Al-Rubeaan KA, Aftab SA, Alotaibi MS, Alghamdi AA, Rafiullah MR. Clinico-laboratory characteristics of diabetic ketoacidosis in adults in a tertiary hospital in Saudi Arabia. *Eur Rev Med Pharmacol Sci*. 2011;15:1120–1202.

14. Elmehdawi RR, Elmagerhei HM. Profile of diabetic ketoacidosis at a teaching hospital in Benghazi, Libyan Arab Jamahiriya. *East Mediterr Health J*. 2010;16(3):292–299.

15. Naeem MA, Al-Alem HA, Al-Dubayee MS, et al. Characteristics of pediatric diabetic ketoacidosis patients in Saudi Arabia. *Saudi Med J*. 2015;36(1):20–25.

16. Mira SA, Fatani HH, El-Zubeir AG, EL-Sabbagh S. Diabetic ketoacidosis in community population. *Diabetes Care*. 1984;7:528–532.

17. Mira AS, Fatani H, El-Zubeir A, El-Sabbagh S. Diabetic ketoacidosis. A report of 123 Saudi diabetic. *Saud Med J*. 1987;8:364–368.

18. Alourfi Z, Homsi H. Precipitating factors, outcomes, and recurrence of diabetic ketoacidosis at a university hospital in Damascus. *Avicenna J Med*. 2015;5:11–15.

19. Gosmanov AR, Gosmanova EO, Dillard-Cannon E. Management of adult diabetic ketoacidosis. *Diabetes Metab Syndr Obes*. 2014;7:255–264.

20. Umpierrez G, Freire AX. Abdominal pain in patients with hyperglycemic crises. *J Crit Care*. 2002;17(1):63–67.

21. Kitabchi AE, Umpierrez GE, Murphy MB, et al. Hyperglycemic crises in diabetes. *Diabetes Care*. 2004;27(suppl 1):S94–S102.