

Diabetic ketoacidosis in Saudi Arabia: factors precipitating initial admission and readmission

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BACKGROUND: Diabetic ketoacidosis (DKA) is one of the complications of diabetes mellitus (DM), primarily type 1 DM. To our knowledge, only one study explored DKA readmission rates in Saudi Arabia.

OBJECTIVES: Identify and analyze precipitating factors for DKA admission and readmission.

DESIGN: Medical record review.

SETTING: Tertiary care center.

PATIENTS AND METHODS: We identified all patients aged 15 years and older admitted with DKA from 2018 to 2020. Descriptive factors and uni- and multivariate analyses are presented for associations with initial admission and readmission.

MAIN OUTCOME MEASURES: Relationships between precipitating factors and initial admission and readmission.

SAMPLE SIZE: 176 patients.

RESULTS: Most of the patients had type 1 DM (n=157). The median (interquartile percentiles) for duration of DM was 6.0 (1.0-12.0) years. The mean (SD) HbA1C (%) was 11.8 (2.6). The factors that precipitated DKA were most commonly treatment nonadherence (55.1%), followed by infections (31.8%) and nonadherence to diet (25.6%). The most common symptoms were nausea and vomiting (87.5%), followed by abdominal pain (72.7%). During the study period, 32.4% of the sample were readmitted with DKA. The median (interquartile range) duration between the first and second admission was 12 (4-25) weeks. In the multivariate analysis, increased odds of readmission for DKA were associated with type 1 DM and medication nonadherence ($P=.038$, $P=.013$, respectively). The severity of the initial DKA and the control of DM were not associated with the readmission rate.

CONCLUSION: Treatment nonadherence is the leading precipitating factor of DKA in our region. Patient education and counseling play a major role in addressing this preventable complication and its medical and financial burden. We advocate more efforts dedicated toward patient education and logistic support.

LIMITATIONS: Retrospective- single center.

CONFLICT OF INTEREST: None.

Diabetes mellitus (DM) is an important cause of multiple health problems that burden the healthcare system. According to the International Diabetes Federation (IDF), Globally, Saudi Arabia is the seventh country in the incidence of DM.¹ Diabetic ketoacidosis (DKA) is an important complication of DM and one of the most common endocrine emergencies.² It involves insufficient insulin levels and an increase in insulin counter-regulatory hormones and peripheral insulin resistance that eventually leads to hyperglycemia, high ketone levels, acidemia, electrolyte imbalance, and dehydration.³ Patients frequently present with abdominal pain, nausea, vomiting, and fruity-scented breath. In addition, some patients can also present with the classic symptoms of DM, such as excessive urination and thirst.⁴ Factors precipitating DKA may include nonadherence to medications, infections, physical or emotional trauma, and the use of medication known to increase blood glucose levels, such as corticosteroids.⁵ The mortality rate following a single episode of DKA is reported to be 5.2%, and it rises by 6-fold with five or more admissions of DKA.⁶ Readmission rates for DKA have increased dramatically over the past two decades.⁷ This study aims to identify rates of readmission of DKA and precipitating factors in an academic center in Jeddah, Saudi Arabia. To our knowledge, there are only a few Saudi publications exploring DKA readmission rates.

PATIENTS AND METHODS

We reviewed the medical records of all patients who were admitted through the emergency department with DKA from 1 January 2018 to 31 December 2020. We included patients older than 15 years of age. The diagnosis of DKA was defined by the following criteria: blood glucose level of >250 mg/dL, serum bicarbonate (HCO_3^-) level ≤ 18 mEq/L, pH <7.30, and ketonemia.⁸ Severe DKA was defined as a DKA with a pH <7.0, with or without ICU admission. ICU admissions to manage the precipitating cause of the DKA, such as septic shock were not considered as severe DKA. The study was approved by the Research Ethics Committee of King Abdul-Aziz University (Reference No 1116-21).

Data collected consisted of patient demographic and disease-related characteristics. For the demographics, we included age, gender, and nationality. For the disease-related data, we included the duration of admission, the precipitating cause, and the presenting symptoms. Also, we included data regarding DKA-related ICU admission and the history of DM (whether it was their first presentation or not, the type and duration of DM, and the medications used for DM man-

agement). Laboratory tests (latest HbA1C, lactic acid and blood pH levels), complications such as renal impairment and cerebral edema were also included. We checked the readmission history and the duration between the first and second admission, along with the precipitating factors for the second admission. Finally, cause of death was determined, if applicable.

The duration of DKA admission was assigned based on the resolution of DKA and not on the end of the admission period, which might extend to manage the precipitating factor such as infection rather than the DKA itself. Resolution of DKA was defined as pH > 7.30, anion gap 10 ± 2 , $\text{HCO}_3^- > 18$, and ability to tolerate oral intake as judged by the admitting medical team as resolution of DKA with change to subcutaneous insulin.

Data were analyzed using IBM SPSS version 26.0 (Armonk, New York, United States: IBM Corp). Descriptive statistics (mean, standard deviation, frequencies and percentages, median, interquartile percentiles) were used to describe the quantitative and categorical variables. Pearson's chi-square test and odds ratios were used to test and measure the association between the categorical study variables and outcome variable (history of readmission). Multivariate stepwise binary logistic regression was used to identify the independent variables associated with history of readmission. A *P* value of $\leq .05$ and 95% confidence intervals were used to report the statistical significance and precision of results.

RESULTS

Of 491 admissions reviewed, 176 met the inclusion criteria. The others were excluded because of young age or incomplete data. Saudi patients accounted for 55.1% of the sample (**Table 1**). The most common age group was 21 to 40 years of age (44.3%), followed by 15 to 20 years (32.4%). Fifty (10.1%) were admitted to the ICU. Type 1 DM was predominant (89.2%) (**Table 2**). The median (IQR percentiles) duration of DM was 6.0 (1.0-12.0) years. The mean (SD) HbA1C was 11.9 (2.6) in 127 patients.

The clinical presentation predominantly involved gastrointestinal symptoms, mostly nausea and vomiting, reported by 154 patients followed by abdominal pain 128 (72.7%), and osmotic symptoms such as polyuria in 41 (23.3%) and polydipsia 35 (19.9%) (**Table 3**). These symptoms were more prevalent in younger age groups ($P = .007$). Nonadherence to medications was the most common precipitating factor, occurring in 97 (55.1%) patients, while infections were the second leading factor that contributed to DKA (31.8%) (**Table**

Table 1. Demographic characteristics of diabetic ketoacidosis patients (n=176).

Gender	
Female	87 (49.4)
Male	89 (50.6)
Nationality	
Saudi	97 (55.1)
Non-Saudi	79 (44.9)
Age (years)	
15-20	57 (32.4)
21-40	78 (44.3)
41-60	28 (15.6)
61-80	9 (5.1)
>81	4 (2.3)

Data are n (%).

4). Patients who had DKA as their first presentation of DM accounted for 16.5%. Likewise, these findings were also evident for the second admission in 42 patients (73.7%) with insulin nonadherence, in 17 (29.8%) for infections, in 19 (33.3%) for diet nonadherence. Complications of DKA such as acute kidney injury were documented in 16 (12.5%) patients, while no patient had developed cerebral edema. Thirteen deaths occurred, all unrelated to DKA; causes included stroke in one patient, underlying malignancies in 3 patients, and COVID-19 pneumonia in 2 patients. There was no difference in the mortality rate between the two types of DM ($P=.635$). The median length of hospital stay was 2 days, and was similar for both types of DM. Patients aged between 41 to 60 years had a longer median length of hospital stay than other age groups ($P=.011$). However, length of hospitalization was unrelated to the mortality rate ($P=.09$).

Out of 176 patients, 57 (32.4%) had a history of readmission with DKA during the study period. After excluding 3 outlier (95, 95, and 96 weeks) the calculated median length of time between the first and second admission was 12 weeks (interquartile range, 4-24 weeks). During the study follow-up period, 88% of the readmissions were in patients younger than the age of 40 years. Of whom 38.6% (22 patients) were aged between 15 to 20 years, and 50.9% (29 patients) were aged between 21 to 40 years. The remaining age groups: 41-61 and 61-80 years had 8.8% (5 patients) and 1.8% (1 patient), respectively. However, none of the patients older than the age of 80 years were re-

Table 2. Diabetes history of diabetic ketoacidosis patients (n=176).

Type 1 diabetes	157 (89.2)
Type 2 diabetes	19 (10.8)
Type of treatment	
Insulin only	125 (71)
Oral hypoglycemic agents only	10 (5.7)
Both insulin and oral hypoglycemic agents	8 (4.5)
None	33 (18.8)
Duration of diabetes (years)	
<8 years	91 (51.7)
≥8 years	85(48.3)
Length of hospital stay (days) for the first episode	
For type 1 diabetes	2 (1-3) ^a
For type 2 diabetes	2 (2-3) ^a
pH blood levels at the first admission (n=153)	
pH of more than 7.00	129 (84.3)
pH of less than 7.00	24 (15.7)
HbA1C (%) at the first admission (n=127)	11.9 (2.6) ^b
HbA1C of more than or equal to 10%	104 (81.9)
HbA1C of less than 10%	23 (18.1)
History of readmission (n=57)	
Type 1 diabetes	56 (98.2)
Type 2 diabetes	1 (1.8)

Data are n (%) or ^amedian (interquartile percentiles) or ^bmean (standard deviation). For HbA1C (%), data was available for 127 patients.

admitted as 3 out of 4 of them died. Factors found to be statistically significant and correlating with risk of DKA readmission on univariate analysis were type 1 DM ($P=.007$), younger age ($P=.043$), and nonadherence to medications ($P=.005$) (**Table 5**). The odds of readmission were 9.98 times more in Type I DM subjects when compared with Type II DM subjects. The odds of readmission were 2.56 times more in subjects who were nonadherent to medications when compared with those who were adherent to medications.

In the multivariate analysis, type 1 DM ($P=.03$) and nonadherence to medications ($P=.01$) were independently associated with the risk of DKA readmission

Table 3. Clinical presentation of diabetic ketoacidosis patients (n=176).

Gastrointestinal symptoms	
Abdominal pain	128 (72.7)
Nausea and vomiting	154 (87.5)
Osmotic symptoms	
Polyuria	41 (23.3)
Polydipsia	35 (19.9)
Polyphagia	10 (5.7)
Weight loss	19 (10.8)
Neurological symptoms	
Loss of consciousness	9 (5.1)
Seizure	1 (0.6)
Headache	9 (5.1)
Altered mental status	10 (5.7)
Miscellaneous	
Fatigability	48 (27.3)
Shortness of breath	30 (17)
Blurred vision	4 (2.3)
Others ^a	53 (30.1)

Data are n (%). ^aSymptoms related to the original precipitating factor for DKA.

Table 4. Precipitating factors for first presentation of diabetic ketoacidosis (n=176).^a

Nonadherence to medications	97 (55.1)
Infections or wounds	56 (31.8)
Nonadherence to diet	45 (25.6)
First presentation of DM	29 (16.5)
Use of medications known to increase blood glucose	2 (1.1)
Insulin administration-related issues	1 (0.6)
Pregnancy	1 (0.6)
Pancreatitis (n=16)	5 (31.3)
Acute kidney injury (n=16) ^b	5 (31.3)
Stroke (n=16)	3 (18.8)
Acute coronary syndrome (n=16)	3 (18.8)
Miscellaneous	16 (9.1)

Data are n (%).^a60 had more than one precipitating factor for the same episode of DKA. ^bIn patients with chronic kidney disease.

(**Table 6**). The adjusted odds of readmission was 8.82 times more in type I DM patients when compared with Type II patients. The odds of readmission were 2.37 times more in subjects who were not adherent to medications when compared with subjects who were compliant to medications.

DISCUSSION

In this study, we found insulin nonadherence to be the primary precipitating factor for DKA, followed by infections. Readmission with DKA during the study period was documented in 32.4% of the patients. Type 1 DM and medication nonadherence were statistically significant factors in increasing the odds of readmission. The majority of patients in the present study were type 1 DM patients, whereas only 11% were diagnosed with type 2 DM, which is similar to multiple studies worldwide. Similarly, Roussel et al concluded that type 1 DM represented most of their sample; 9 type 2 DM frequency was more than that of our study (31%). To the contrary, in countries with different genetic and socio-economic backgrounds, such as studies by Seth et al, in India, and Shahid et al, in Pakistan, type 2 DM was the most prevalent type in patients admitted with DKA, and the mean age of patients was 51.46 and 52 (11) years, respectively.^{4,10} The higher mean age in the two studies may be explained by the fact that type 2 DM was more prevalent in their studies, and as known type 2 DM most frequently occurs in older age. Patients aged between 21 to 40 years represented most of our sample, which favors type 1 DM as triggering DKA development in our study rather than type 2 DM. Likewise, in another study from Russia, Dzherieva et al, patients had a mean age of 36 (0.93) years.¹¹

The percentage of newly diagnosed patients with DM presenting for the first time with DKA varies between countries. Our study showed that 16.5% of patients (age 15 years or older) were admitted with DKA as their initial presentation of DM. This finding was also reported in another study from the Middle East, where 34 out of 160 patients (age 20 years or more) had DKA as their first presentation of DM.¹² In the current study, DKA was more prevalent in patients with poorly controlled DM. The HbA1C of more than 10% contributed to a four times greater risk of DKA in a local study conducted in Riyadh.¹³ Two other reports, where the mean of HbA1C was 12.1% (2.7%) and 11.7% (2.9%), reached to a similar conclusion.^{14,15} The study in Riyadh reported that females had higher incidence of DKA admission.¹³ Gender did not impact the occurrence of DKA in our study, which is supported by what has been described in a recent systematic review.¹⁶

Table 5. Factors associated with readmission for diabetic ketoacidosis subjects (univariate analysis).

	History of readmission No. (%)		χ^2 -value	P value	Unadjusted odds ratio (95% CI)
	Yes (n=57)	No (n=119)			
Age groups					
15-20	22 (38.6)	35 (61.4)	8.142	.043	7.54 (0.92-62.12)
21-40	29 (37.2)	49 (62.8)			7.10 (0.88-57.48)
41-60	5 (17.9)	23 (82.1)			2.61 (0.27-24.94)
>60	1 (7.7)	12 (92.3)			1.0 (ref.)
Gender					
Female	32 (36.8)	55 (63.2)	1.518	.218	1.49 (0.79-2.89)
Male	25 (28.1)	64 (71.9)			1.0 (ref.)
Type of DM					
Type I	56 (35.7)	101 (64.3)	7.156	.007	9.98 (1.30-76.75)
Type II	1 (5.3)	18 (94.7)			1.0 (ref.)
Duration of diabetes					
<8 year	28 (30.8)	63 (69.2)	0.225	.635	1.0 (ref.)
≥8 year	29 (34.1)	56 (65.9)			1.16 (0.62-2.19)
Length of hospital stay at first episode					
<3 days	38 (35.5)	69 (64.5)	1.219	.270	1.0 (ref.)
≥3 days	19 (27.5)	50 (72.5)			0.69 (0.36-1.33)
Severe DKA at first admission					
Yes (pH<7.0)	8 (33.3)	16 (66.7)	0.001	.999	1.0 (0.40-2.52)
No (pH≥7.0)	43 (33.3)	86 (66.7)			1.0 (ref.)
DM control at first episode					
Poor control (HbA1C≥10)	4 (28.6)	10 (71.4)	0.101	.751	0.82 (0.25-2.74)
Mild-to-moderate control (HbA1c<10)	53 (32.7)	109 (67.3)			1.0 (ref.)
Nonadherence to medications					
Yes	40 (41.2)	57 (58.8)	7.731	.005	2.56 (1.31-5.01)
No	17 (21.5)	62 (78.5)			1.0 (ref.)
ICU admission at first episode					
Yes	17 (34.0)	33 (66.0)	0.083	.773	1.11 (0.55-2.22)
No	40 (31.7)	86 (68.3)			1.0 (ref.)
Infections/wounds					
Yes	19 (33.9)	37 (66.1)	0.089	.765	1.11 (0.56-2.17)
No	38 (31.7)	82 (68.3)			1.0 (ref.)

Data are n (%).

Table 6. Factors independently associated with readmission in diabetic ketoacidosis subjects (by stepwise multivariate logistic regression).

	B	S.E.	Wald χ^2	P value	Odds ratio	95% CI odds ratio	
						Lower	Upper
Type of diabetes	2.177	1.047	4.324	.038	8.816	1.133	68.575
Adherence to medications	.864	.349	6.134	.013	2.373	1.198	4.703
Constant	-3.290	1.051	9.806	.002	.037		

Dependent variable (History of readmission-Yes/No). Reference levels: type 1 DM, nonadherence. Non-significant variables in the model: age groups, gender, hospital length of stay, duration of DM, HbA1C groups, ICU admission and Infection/wounds. Model summary measures: deviance 213.755, Cox and Snell R2 0.044, Nagelkerke R2 0.061

Medication nonadherence was the leading factor leading to DKA in our study. Conversely, studies from India and Damascus showed that infections most often precipitated DKA.¹⁷⁻¹⁹ Indeed, the occurrence of DKA is influenced by multiple factors, including patient awareness about the disease, socioeconomic factors, and the health care provided for the patient.²⁰ Some patients may consider quitting medications after they return to fair health or during the “honeymoon” period after a recent diagnosis of type 1 DM.²¹ Furthermore, among other infectious diseases, pneumonia and urinary tract infections were more prevalent in contributing to DKA than other infections. Notably, some of our patients had more than one precipitating factor, such as medication nonadherence coupled with infections. This finding was also reported by Seth et al.^{4,10}

Previous studies have indicated that the odds of DKA readmission are increased in patients aged younger than 35 years, particularly females, or any patient with a history of depression or substance abuse, especially when insurance is self-paid or pays little of the expense. Patients with a longer duration of diabetes also had a higher odds of recurrent DKA in another study.²² The current study found that the duration of diabetes and gender were not significantly related to the readmission rate. Remarkably, the readmission rate was related to type 1 DM and younger adult age, mainly younger than 40 years. This finding is supported by studies from the United States and the Middle East.^{23,24} In our study, 32.4% of patients had a history of a subsequent admission with DKA within a 3-year-follow up period. Another study from the Middle East in 2020 had a similar rate of readmission of 31%.¹² They also found that young age (odds ratio 102, 95% CI, 1.00-1.04), an established history of DM (odds ratio 1.25, 95% CI, 1.7-18) and poorly controlled DM (odds ratio 1.25, 95% CI 0.68-0.96) increased the odds of readmission with DKA.¹² In our analysis, having a severe first episode of DKA as evident by pH<7.0, or significantly

uncontrolled DM as evident by high HbA1C of 10% or more did not correlate with readmission rate. This is similar to findings from studies from the United States by Bradford and colleagues that found no correlation between baseline poorly controlled diabetes and risk of DKA readmission. They also categorized the risk of readmission by groups and found that patients with combined poorly controlled DM, depression, no private insurance, and with a history of substance abuse or alcoholism have the highest risk of readmission (86.7%) in comparison to individuals having none of these factors (11.1%).²³

Educating patients with DM about the factors most often associated with precipitating DKA, reinforcing the need to comply with medication recommendations, and educating patients about sick day management are essential tools to reduce admission rates, decrease complications and limit hospital stay and costs. In addition, patients with chronic illnesses such as DM require a multidisciplinary team approach to offer the proper logistic, social and psychosocial support for those vulnerable patients.²⁵

The mortality associated with DKA was low. All deaths in the current study were unrelated to DKA and were instead related to the illness that precipitated DKA, such as COVID-19 pneumonia and myocardial infarction. Mortality rates are reported to range from 7% to 9% in some international studies.^{12,25} Studies by Usman et al, and Mahesh et al, reported high rates of deaths, up to 17.6 % and 16.3%, respectively, which might be attributed to many factors mentioned in these studies such as old age, comorbidities, dehydration and the severity of DKA.^{21,26} Similar to the present study, a local publication from Riyadh did not report any deaths related to DKA.²⁷ Although DKA complications are not commonly reported, 12.5% of our study patients developed acute kidney injury, and no cerebral edema was documented. Most studies that reported a high incidence of such complications were

conducted among children and not adults.^{28,29}

This study has a few limitations, one of which is that it was a retrospective record review with a relatively small sample size. It was conducted in a single center and thus probably does not represent the population of the region. Strengths of this study were the consistent definition of DKA and manual retrieval of medical records, which specifically documented that the presentation was related to DKA itself or that DKA was a consequence of a major illness such as septic shock or stroke. In addition, the careful examination of

the underlying cause of death in those patients and identification of the accurate duration of DKA admission from diagnosis until resolution are also strengths. In conclusion, treatment nonadherence was the leading precipitating factor for DKA followed by infections. Almost one-third of the patients were readmitted at least once and the main risk factor was also medication nonadherence. All mortalities were not directly related to DKA but rather to the severity of illness that precipitated the DKA. We advocate more efforts dedicated toward patient education and logistic support.

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