



Research Article

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## ***Contributing Clinical Presentation, Risk Factors, and Outcomes for Diabetic Ketoacidosis Patients: A Single-Center Retrospective Study***

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### **ABSTRACT**

*In patients with diabetes mellitus, diabetic ketoacidosis (DKA) is the most common acute metabolic complication and occurs more frequently in those with type 1 diabetes (DM1). DKA is a hyperglycemic crisis that develops due to insulin insufficiency. It can be due to insulin noncompliance, newly diagnosed diabetes mellitus, a subtherapeutic dose, and conditions that cause hyperglycemia leading to elevated ketone bodies (e.g., urinary/respiratory tract infections), and some drugs. As reported by the World Health Organization in 2014, Saudi Arabia ranks seventh highest in the world for diabetes prevalence. The high prevalence of diabetes in Saudi Arabia contributes to the high incidence of patients with DKA.*

*To evaluate the precipitating risks of DKA in diabetic patients and its clinical presentation and outcomes at King Faisal Hospital at Makkah in Saudi Arabia. A retrospective review of patients with (DM1) at King Faisal Hospital in Makkah who presented with DKA from September 2020 to February 2022 was performed. Symptoms and risk factors were compared across age and sex. We found that the symptoms of polyuria, nausea and vomiting, weight loss, and fever significantly differed at the 10% level depending on the patient's age. No signs were statistically significant concerning sex. Of the precipitating factors, patient failure to comply, inadequate insulin dose, and infections were statistically significant in the older age group. It was observed that missed insulin doses, high random blood sugar, and pH less than 7.3 were the most significant predictors of DKA recurrence.*

**Key words:** DKA, Diabetes, Insulin, DM1

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### **INTRODUCTION**

Diabetes Mellitus (DM) is a group of glucose metabolism characterized by high blood glucose levels [1]. There are both short and long-lasting impacts of this long-term, chronic illness. Besides, hyperosmolar hyperglycemia and diabetic ketoacidosis are the most feared DM complications, requiring immediate medical intervention. Diabetic ketoacidosis (DKA) is a more rampant illness that could result in a person with type one diabetes [2]. During the first day of hospitalization, simple clinical and laboratory variables can be used to confirm diabetic ketoacidosis patients [3]. DKA usually occurs due to minimized insulin levels and more concentrated counter-regulatory hormones, resulting in hyperglycemia, acidemia, and ketonemia [4]. DKA can cause severe alteration

of the body's metabolism, impacting both carbohydrates and fats as well as proteins. The body reaches a catabolic state with an excessive breakdown of glycogen stores, deployment of amino acids, and triglyceride hydrolysis. As a result, it leads to the continuous production of glucose and ketone bodies in the liver, exacerbating metabolic decompensation [5].

The most famous acute biochemical metabolic complication noticed is Diabetic ketoacidosis (DKA). It is common in patients with diabetes mellitus and occurs more frequently in those who have developed type 1 diabetes. DKA is a challenge of hyperglycemia due to fat emulsification at an excessively rapid rate. Through Lipolysis, Fat is broken by the liver ketone, a form of energy that assists blood acid development [6, 7].

Insulin noncompliance, subtherapeutic dose, and infection are the most common factors precipitating DKA [8] Tran. Another factor is the underlying medical conditions that cause hyperglycemia leading to elevated ketone bodies (e.g., trauma, urinary tract infection, respiratory tract infections, sepsis, and heart attack). In addition, medications that impact the breakdown of glucose components, like agents of thiazides, could lead to DKA [9]. Diabetic ketoacidosis is more likely to occur in the early stages of diabetes than at any other time. DKA is present in approximately one-third of instances with untreated diabetes mellitus. DKA can occur within a few hours following the precipitating incident [10]. Poor socioeconomic position, teenage age (13 to 25 years old), gender, high HbA1C levels, prior diabetes, and mental health concerns (such as an eating disease) all have been tied to an increased chance of developing diabetes ketoacidosis [11-13].

DKA can cause symptoms such as dehydration, nausea, abdominal pain, acetone breath, and Kussmaul breathing. A common symptom is a general exhaustion with no apparent cause [14]. Despite the illness, some DKA patients maintain an average temperature or even hypotension [15]. Managing hypovolemia and diabetes, as well as doing a comprehensive investigation into the cause of the DKA, are all critical components of DKA treatment [16]. Possible prevention strategies are proposed, including the specification of those with a high chance of being in a nonmodifiable social human population. Some of the adjusted risk factors of diabetes personal management learning can be used as a second strategy for risk mitigation [11].

According to research, structured education is associated with lower rates of DKA. This experience of knowledge of the risk element of effective strategies is critical for identifying subgroups of people at high risk of DKA. It should also be applied in considering a higher DKA risk of therapy options. The most vital clinical task is to prevent DKA in an inpatient with type one diabetes, which addresses Sodium-glucose co-transporter (SGLT) inhibitors therapy [11]. According to the Centers for Disease Control and Prevention (CDC)-the United States advocates that Diabetes Surveillance System, DKA hospitalization rates increased significantly during 2009–2014. According to Health Organization, Saudi Arabia was ranked seventh highest in the world for diabetes prevalence, a report that was given in 2014. The high prevalence of diabetes in Saudi Arabia results in the highest incidence of DKA admissions. A previous study evaluated the risk factors that could result in the standard metabolic diabetic disease increment of people who identified several underlying infections in approximately 40% of patients. In another 30% of patients, DKA developed as diabetes mellitus (DM) had not been diagnosed, and 22% had missed or taken an insufficient insulin dose [10].

During the research conducted at King Abdulaziz Medical City in Jeddah from January 2010 to June 2016, DKA frequently occurred in young women with poor medication adherence [17]. Retrospective research carried out in Saudi Arabia, Riyadh, found that an increased chance of developing DKA is associated with high levels of HbA1c, prolonged blood sugar level, adolescent stage, female sex, and nonattendance at hospital appointments [18]. Patients also developed DKA due to undiagnosed DM, and 22% of the patients had missed a dose or taken an insufficient amount of insulin [10].

Although Saudi Arabia is one of the three countries in the region with the highest frequency of DKA presentations, only a few studies have focused on describing and quantifying the occurrence of DKA. The study's primary purpose is to examine the precipitating danger of DKA to the diseased person with diabetes who was admitted to King Faisal Hospital in Makkah and evaluate its clinical presentation and outcomes.

## MATERIALS AND METHODS

According to the research review study of DKA patients with DM1 who were registered and followed up at King Faisal Hospital in Makkah, data were extracted only for those diagnosed with DKA and taken to the hospital for treatment and prevention in September 2020 and February 2022. Other forms of diabetes, hyperosmolar hyperglycemic state, and patients with no information were excluded (**Figure 1**). The characteristics of DKA were

categorized as slight, reasonable, or superficial according to the following limitations: plasma glucose, arterial pH, serum bicarbonate, urine ketone, and serum ketone levels; and anion gap (Table 1).

**Table 1.** Criteria and classification of DKA

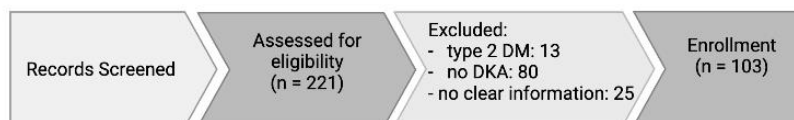
DKA	Mild	Moderate	Severe
Plasma glucose (mg/dL)	>250 mg/dL	>250 mg/dL	250 mg/dL
Arterial pH	7.25–7.30	7.00–7.24	<7.00
Serum bicarbonate (mEq/L)	15–18	10–15	<10
Urine ketone*	+	+	+
Serum ketone*	+	+	+
Effective serum osmolality**	Variable	Variable	Variable
Anion gap***	>10	>12	>12
Mental status	Alert	Alert/drowsy	Stupor/coma

Note: From Diabetic ketoacidosis - end text - NCBI bookshelf. (n.d.). Retrieved May 14, 2022, from <https://www.ncbi.nlm.nih.gov/books/NBK279146/>.

*Data description*

The dataset consisted of 103 patients and 33 variables. The variables included sociodemographic variables such as age and sex and clinical variables such as body mass index (BMI), number of DKA episodes, infection, mental state, precipitating factors, manifestations, pH, and HCO<sub>3</sub> values. The sample set comprised 60.2% males, and 76.7% of patients were 18 years of age or older. Their average BMI was 23.59 kg/m<sup>2</sup> (SD = 4.53), and the average random blood sugar result was 451.45 mg/dL (SD = 197.96).

Flow-process diagram



**Figure 1.** Flow Diagram for Inclusion and Exclusion criteria

**RESULTS AND DISCUSSION**

*Clinical presentation of DKA*

The symptoms of the patients were compared for age and sex. The age groups analyzed were <18 years of age and ≥18 years of age. The results of the comparison of the symptoms for age and sex are presented in (Table 2).

**Table 2.** Patient symptoms by age in years and sex at the time of presentation with ketoacidosis of diabetes (N = 103).

Symptoms	Age < 18	Total patients n (%)	Age ≥ 18	P- value	Male	Female	P- value
<b>Polyurea/Polydipsia/Polyphagia</b>	6 (42.86%)	14 (13.73)	8 (57.14%)	0.06	11 (78.57%)	3 (21.43%)	0.123
<b>Weight loss</b>	2 (66.67%)	3 (2.94)	1 (33.33%)	0.07	3 (100.00%)	0 (0.00%)	0.149
<b>Abdominal pain</b>	13 (28.89%)	45 (44.12)	32 (71.11%)	0.26	24 (53.33%)	21 (46.67%)	0.236
<b>Nausea and vomiting</b>	18 (24.32%)	74 (72.55)	56 (75.68%)	0.01	14 (18.91%)	60 (81.08%)	0.008
<b>Dizziness</b>	3 (20.00%)	15 (14.71)	12 (80.00%)	0.73	8 (53.33%)	7 (46.67%)	0.580

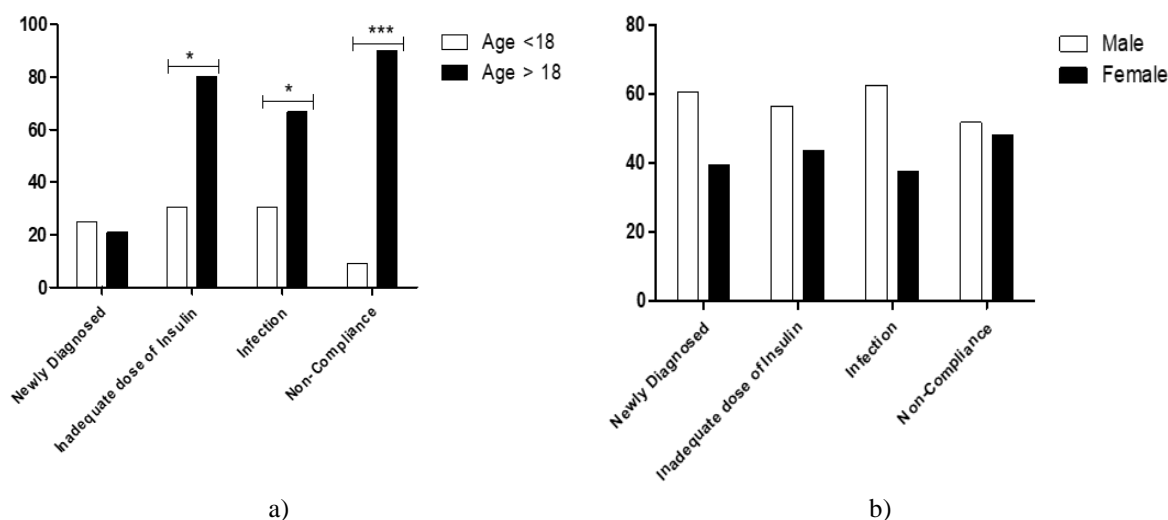
<b>Fever</b>	0 (0.00)	6 (5.88)	6 (100.00%)	0.01	4 (66.67%)	2 (33.33%)	0.724
<b>Mental state</b>	1 (0.17%)	6 (5.88)	5 (0.83%)	0.69	5 (0.83%)	1 (0.17%)	0.222
<b>Others</b>	10 (22.73%)	44 (43.14)	34 (77.27%)	0.87	25 (56.82%)	19 (43.18%)	0.592

As shown in (Table 2), nausea and vomiting were the most predominant clinical presentations of DKA in the older age group ( $P$ -value < 0.01) and in female subjects ( $P$ -value < 0.008). Polyurea was most crucial in the older adults (57.14%) and not significantly different ( $P = 0.123$ ) by sex. Weight loss was more predominant in the younger age group (66.67%,  $P$ -value < 0.10). No significant difference in abdominal pain, dizziness, fever, and mental state symptoms were found concerning age or sex.

*Risk factors precipitating DKA*

The factors precipitating the development of DKA in patients were compared for different age groups and by sex. The comparison of symptoms concerning age and sex is presented in (Figure 2).

None of the patients was left out when determining the increased growths of DKA. Missed insulin dose (noncompliance) was recorded in 91% of patients with DKA in the worn-out age group and was the most significant precipitating risk factor among this group. Inadequate insulin dose and existing disease-causing organisms had higher chances of occurring in those who have grown older. It was found that none of the statistically crucial distinctions amongst the studied precipitating determinants related to the development of DKA concerning sex.



**Figure 2.** Risk factors precipitating diabetic ketoacidosis (N = 103)

*Predictors of outcome*

Predictors of outcome were compared using unadjusted odds ratios, and the results are presented in (Table 3).

**Table 3.** Determinant of the result of ketoacidosis (N = 103)

Predictors of outcome	Outcome		Odds ratio (CI)	P-value
	Total number of DKA episodes ≤ 1 (n = 71)	Total number of DKA episodes > 1 (n = 32)		
<b>Age</b>				
<18	16 (15.5%)	8 (7.8%)	0.873 (0.329, 2.313)	0.784
≥18	55 (53.4%)	24 (23.3%)		
<b>Sex</b>				
Female	25 (24.3%)	16 (15.5%)	0.543 (0.233, 1.268)	0.158
Male	46 (44.7%)	16 (15.5%)		
<b>DMS/comatose</b>				

<b>Conscious</b>	62 (62.6%)	31 (31.3%)	0.000 (0, ∞)	0.999
<b>Not conscious</b>	6 (6.1%)	0 (0.0%)		
<b>Inadequate dose of insulin</b>				
<b>Insulin taken</b>	9 (15.2%)	7 (9.8%)	1.373 (0.516, 3.654)	0.014
<b>Insulin missed</b>	62 (51.1%)	25 (23.9%)		
<b>Fever</b>				
<b>No</b>	64 (62.7%)	32 (31.4%)	0.000 (0, ∞)	0.999
<b>Yes</b>	6 (5.9%)	0 (0.00%)		
<b>Random blood sugar</b>				
<b>&lt;300 mg/dL</b>	5 (14.4%)	3 (6.2%)	1.057 (0.362, 3.084)	0.012
<b>≥300 mg/dL</b>	66 (54.6%)	29 (24.7%)		
<b>pH</b>				
<b>≥7.3</b>	29 (28.4%)	5 (13.7%)	1.818 (0.781, 4.231)	0.016
<b>&lt;7.3</b>	41 (40.2%)	27 (17.6%)		
<b>Bicarbonate</b>				
<b>≥15</b>	43 (42.2%)	18 (17.6%)	1.239 (0.530, 2.893)	0.621
<b>&lt;15</b>	27 (26.5%)	14 (13.7%)		
<b>Urine ketones</b>				
<b>Negative</b>	42 (41.6%)	14 (13.9%)	1.821 (0.776, 4.278)	0.169
<b>Positive</b>	28 (27.7%)	17 (16.8%)		
<i>CI; Confidence Interval, (p &lt; 0.001)</i>				

The outcome variables were dichotomized based on the total number of DKA episodes ( $\leq 1$  or  $> 1$ ). As shown in the above table, none of the considered predictors was significantly associated with the outcome. The 95% confidence intervals of the estimate of odds ratio contained the value unity, and as such, the estimated odds ratios are not statistically significant for this sample.

Patients who had shown the features of  $\geq 1$  DKA episode were comparable to those with  $> 1$  DKA episode. Missed insulin dose, high random blood sugar, and  $\text{pH} < 7.3$  are predictors of DKA recurrence. As shown in (Table 3), these differences were statistically significant.

DM is an endocrine condition that can cause various complications, including hyperosmolar hyperglycemia and diabetic ketoacidosis. DKA is characterizable by many features, including vomiting, nausea, and pain in the abdominal regions. Elevated dehydration of the mouth and excessive discharge of urine are also symptoms. Kussmaul's inhalation of air and the foul smell are two distinct symptoms of DKA [19]. Many triggers have been described, including missing an insulin dose and ongoing infection [20]. As per the clinical result, DKA is determined by the patient's behavior to first health care, the cause of DKA, together with the parameter results of biochemical. Advanced age, bedridden status, and mechanical air conditioner use are self-dependent predictors of the 30-day death rate [21].

Consequently, in this research, we aimed to evaluate the clinical presentation of DKA symptoms in patients by age and sex. We also aimed at the risk factors precipitating diabetic ketoacidosis. Finally, we majored in the determinant of the results of ketoacidosis diabetes.

Our results showed that nausea and vomiting were the predominant clinical presentations of DKA in the highest age group and female subjects. In contrast, polyuria/polydipsia/polyphagia was highly important in those who are mostly considered older people and was significantly indifferent concerning sex. Weight loss was more prominent in the younger age group. There was no significant difference in abdominal pain, dizziness, fever, and mental state symptoms concerning age and sex. A prospective observational study by Ahuja et al. (2019) agreed with our findings: the authors found excessive vomiting of about 32.2% daily, discomfort in the abdomen (27.9%), together with excess stress (26.8%) were the most prevalent clinical symptoms associated with DKA [10]. Shahid et al. (2020) evidenced that cross-sectional observational research was consistent with ours [19]. The more likely prevalent clinical signs were identified to be nausea together with vomiting (57.7%). Abdominal discomfort (42.2%) and dehydration (42.2%) were also identified. In agreement with the previous findings of the study by

Almalki *et al.* (2016) also noted that the most frequent symptoms presented by diabetic patients with DKA were vomiting (79.8%), nausea (70.5%), and abdominal pain (75.8%). Other symptoms were polyuria (26.3%), polydipsia (28.2%), reduced level of consciousness (20.8%), shortness of breath (13.8%), and fever (14.1%) [2]. Our findings suggest that nausea and vomiting were the main clinical presentation of DKA in female subjects. In contrast, polyuria/polydipsia/polyphagia was not significantly different concerning sex. Furthermore, none of the previous studies found significant variations in the clinical presentation of DKA in males and females [10].

Our present results also indicated that when assessing all patients with higher chances of being affected by the growth of DKA, 91% of patients had missed their insulin dose (noncompliance). Significantly when people have grown to older ages, this was the most significant precipitating risk factor among this group. Patients who had taken inadequate insulin doses and pre-existing mutagens had higher chances of being found within the age bracket of people in society. No statistically significant variations were found between the studied precipitating factors associated with DKA development concerning sex. Recently, a descriptive, retrospective study in Saudi Arabia supported our results.

Alhayek *et al.* (2020) found significant associations regarding sex, age, BMI, hemoglobin A1c (HbA1c), diabetes duration, and clinic visits. Female subjects were clearly at a greater risk of DKA [22]. A meta-analysis and systematic review by Bamgboye *et al.* (2021) found that the predisposing variables of DKA in patients with diabetes are excess alcoholic drinks, sexual intercourse, and food shortage resulting in sickness [23]. An Iranian study indicated that diabetic ketoacidosis is most predominant in patients newly diagnosed with diabetes [24]. The majority of the patients had severe DKA. Most female children below the age of 16 have a highly suspected risk of developing severe DKA growth. Our findings also agreed with those of Ahuja *et al.* (2019) [10]. They found that the cause of germs growth and inadequate treatment of insulin, misuse of drug abuse as prescribed in the medication of the patient tablet taken for treatment are one of the predisposing factors for DKA growth. Inadequate insulin dose was more prevalent than underlying infection. Shahid *et al.* (2020) also showed that infection and noncompliance with therapy were the main precipitating factors [19]. Almalki *et al.* (2016) stated that the predominant precipitating factor was noncompliance with an insulin regimen (54.2%) [2].

Our results also showed that missed insulin doses, high random blood sugar, and pH < 7.3 were predictors of DKA recurrence, in agreement with a previous study by Golbets *et al.* (2021) [25]. This study found that patients with HbA1C more than 9.0% and younger age are related to recurrent DKA development. Another study by Shaka *et al.* (2021) showed that high blood pressure, sexual intercourse, and Discharge Against Medical Advice are essential for the recurrent readmission of DKA growth [26]. Lyerla *et al.* (2021) stated that African-American ethnicity, younger age, type 1 DM, history of homelessness, and drug misuse were all predictors of DKA recurrence [27]. In agreement with our results, a retrospective cohort study by Del Degan *et al.* (2019) found that recurrent DKA was related to problems with alcohol or illicit substance misuse and higher glycosylated hemoglobin levels, as well as nonadherence to insulin therapy [28]. Moreover, Almalki *et al.* (2016) found the most crucial difference between men's and women's gender based on recurrent DKA development. Female patients had more hospitalizations for recurrent DKA than male patients [2].

## CONCLUSION

Eight groups of symptoms were compared by age and sex. Of these, we found a significant difference in the symptoms of polyuria, nausea and vomiting, weight loss, and fever at a 10% level regarding the patient's age. Still, these symptoms were not statistically significantly different concerning sex. Four precipitating factors, namely, newly diagnosed diabetes, inadequate insulin dose, infection, and noncompliance, were compared by age and sex. Of these four factors, patient failure to comply, inadequate insulin dose, and infection were statistically significant in the older age group. The predictor's age, sex, mental state, insulin intake, fever, random blood sugar, pH, bicarbonate, and urine ketones were considerable for the outcome of DKA. The odds ratio and their corresponding 95% confidence intervals were considered. It was observable that missed insulin dose, high random blood sugar, and pH < 7.3 were the most significant predictors of DKA recurrence.

### *Clinical implications*

There should be clear awareness of the need to follow up with patients on insulin therapy after diabetes is diagnosable. Globally, studies have identified different variables as the most significant predictors of DKA recurrence. It is needed to develop a recommendable application for frequently updated guidelines to give the side effect of DKA recurrence on a person. DKA onset and recurrence can highly need control through the learning of

healthcare, and pharmacist practitioners are well enabled to enhance patient learning, personal protection, and individualized patient care. Patient learning on personal healthcare management can help avoid DKA development and recurrence [29, 30].

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**CONFLICT OF INTEREST :** None

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**ETHICS STATEMENT :** The Umm Al-Qura University Institutional Review Board assessed and approved the current study protocol (reference number: GFLL011121). Informed permission was not sought, and patients were not directly communicated with during the evaluation of their medical history. Investigators have safeguarded the data's security and the patient's privacy.

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