

# Frequency and associated risk factors of recurrent diabetic ketoacidosis among Saudi adolescents with type 1 diabetes mellitus

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## ABSTRACT

**الأهداف:** دراسة نسبة تكرار الحمض الكيتوني والعوامل المرتبطة به بين المراهقين السعوديين المصابين بالسكري من النوع الأول.

**الطريقة:** أجريت هذه الدراسة المقطعية في مدينة الأمير سلطان الطبية العسكرية، الرياض، المملكة العربية السعودية وذلك خلال الفترة من يناير 2013م إلى مايو 2014م. ولقد شارك في الدراسة 103 مراهقاً مصاباً بالسكري من النوع الأول (13-18 عاماً، 57 ذكراً) ممن تم تنويمهم في المستشفى. ولقد تم إجراء مقابلات مع المشاركين في الدراسة باستخدام استبيان باللغة العربية يحتوي على جميع المعلومات المطلوبة بما في ذلك المعلومات السريرية والديموغرافية.

**النتائج:** لقد أصيب 56 مشاركاً بالدراسة بالحمض الكيتوني مرة واحدة، فيما أصيب 41 بالمرض مرتين، و6 مشاركين عانوا من الحالة  $\geq 3$  مرات. مقارنة مع المراهقين الذين كان لديهم نسبة نسبة السكر التراكمي  $\geq 9\%$ ، تم العثور على اختلافات في نسبة من كان السكر التراكمي لديهم أقل من 9%. وبالمثل كان المراهقين الذين توقفوا عن أخذ جرعات الأنسولين والذين يعانون من الحثل الشحمي في موقع الحقن نسبة تكرار أعلى من الحمض الكيتوني. وأظهرت النتائج أن وقف الأنسولين كان السبب الرئيسي لتكرار الحمض الكيتوني (67%) تليها عدوى التهابات (31%). من بين المراهقين الذين توقفوا عن أخذ جرعات الأنسولين، لم يذكر 31 مريضاً (46.3%) أسباب توقفهم عن أخذ جرعات الأنسولين. فيما لم يأخذ 25 مريضاً (37.3%) الأنسولين نتيجة شعورهم بالمرض، وقد توقف 7 مرضى (10.4%) عن أخذ الأنسولين نتيجة وجود أكثر من سبب من الأسباب التي تم ذكرها، فيما ذكر 4 مرضى (6%) بأن السبب كان في نقص الإمدادات وأسباب أخرى. وكشف تحليل الانحدار أن ارتفاع مستوى نسبة السكر التراكمي ووجود الحثل الشحمي كانا عاملان مستقلان يزيدان من نسبة خطر تكرار الحمض الكيتوني.

**الخاتمة:** يعد كلاً من ارتفاع نسبة السكر التراكمي، ووجود الحثل الشحمي في مكان حقن الأنسولين، والتوقف عن أخذ جرعات الأنسولين من العوامل المستقلة التي تزيد من خطر تكرار الحمض الكيتوني. لذلك توصي الدراسة بزيادة التثقيف الصحي لمرضى السكري وذلك من كافة التخصصات الصحية للتحكم بمثل هذه العوامل لدى المرضى المعرضين لمثل هذه الحالة أكثر من غيرهم.

**Objectives:** To explore the frequency and associated risk factors of recurrent diabetic ketoacidosis (RDKA) among Saudi adolescents with type 1 diabetes mellitus (T1DM).

**Methods:** A cross-sectional study was conducted among 103 T1DM adolescents (aged 13-18 years, 57 males) who were hospitalized for diabetic ketoacidosis

(DKA) between January 2013 and May 2014 at Prince Sultan Military Medical City (PSMMC), Riyadh, Kingdom of Saudi Arabia. The respondents were purposively, conveniently selected, and interviewed using a structured Arabic questionnaire including clinical information and demographics.

**Results:** Fifty-six participants had experienced one episode of DKA, 41 had 2 episodes, and 6 had  $\geq 3$  episodes. Compared with adolescents who had hemoglobin A1c (HbA1c)  $\leq 9\%$ , mean difference in RDKA was found among adolescents with  $>9\%$  HbA1c. Similarly, adolescents who stopped insulin and those with lipodystrophy at the injection site had a higher frequency of RDKA. Discontinuing insulin (67%) was the major reason for RDKA followed by infection (31%). Among adolescents who discontinued insulin treatment, 31 (46.3%) gave no reason for stopping, 25 (37.3%) reported feeling sick, 7 (10.4%) gave a combination of reasons, and 4 (6%) reported a lack of supplies or other reasons. Regression analysis revealed that a higher HbA1c level and the presence of lipodystrophy were independent risk factors for RDKA.

**Conclusion:** The frequency of RDKA was significantly greater in the T1DM adolescents with a higher HbA1c level, lipodystrophy, and those who had discontinued insulin treatment. Comprehensive multidisciplinary diabetes education should be offered to control modifiable risk factors in these patients.

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According to the latest report by the International Diabetes Federation, Saudi Arabia is listed as third among the top 10 countries with the highest prevalence rates of diabetes (3.6 million cases of diabetes).<sup>1</sup> While type 2 diabetes dominates in great numbers, type 1 diabetes mellitus (T1DM) remains an imperative issue. Over the last 3 decades, the incidence rate of T1DM is growing in Saudi Arabia,<sup>2</sup> and the prevalence of T1DM in Saudi Arabian children and adolescents is 109.5 per 100,000.<sup>3</sup> It is well established that adolescents diagnosed with T1DM, face several lifestyle changes and the risk of facing debilitating and life-threatening complications, such as diabetic ketoacidosis (DKA).<sup>4,5</sup> Diabetic ketoacidosis is a recurrent problem with acute complications and is the most common cause of death in adolescents with T1DM.<sup>5,6</sup>

Diabetic ketoacidosis is an acute metabolic complication of diabetes characterized by the triad of hyperglycemia, acidosis, and ketosis that take place in the presence of very low levels of effective insulin action.<sup>7</sup> In some cases, DKA may be the first indication of previously undiagnosed diabetes, but it may often occur in those who already have diabetes as a result of a variety of causes, such as poor compliance with insulin therapy.<sup>8,9</sup> Further, studies stated that infection is the important precipitating cause for DKA worldwide, occurring in 30-50% of cases. Vomiting, dehydration, confusion, deep gasping breathing, and occasionally coma are typical symptoms of DKA. Many studies reported that DKA is the leading cause of mortality in children with T1DM, and is associated with increased morbidity and health care expenditure.<sup>10,11</sup> Longitudinal studies also indicate that 20% of pediatric patients account for 80% of all admissions for DKA, and the incidence of DKA peaks during the adolescent period.<sup>12</sup>

Research shows that recurrent diabetic ketoacidosis (RDKA) rates are dependent on medical services and socioeconomic circumstances of the adolescents.<sup>13</sup> Effective treatment of DKA requires frequent monitoring of patients, replacement of electrolyte losses, modification of hypovolemia and hyperglycemia, and careful search for the precipitating cause. As most DKA cases occur in patients with a known history of diabetes, this acute metabolic complication can be preventable by the education of patients, healthcare professionals, and the general public and frequent self measured blood glucose.<sup>14,15</sup>

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Compared with the developed countries, the dearth of research currently available on the frequency, associated risk factors of RDKA, as well as the socio-demographic properties of RDKA certainly warrants concern, particularly the lack of appropriate studies in this specified area in Saudi Arabia. Hence, we conducted this study to investigate the frequency and associated risk factors of RDKA among Saudi adolescents with T1DM.

**Methods. Study design and setting.** This cross-sectional study was conducted among 103 T1DM adolescents (aged 13-18 years at the last visit) who were hospitalized for DKA management between January 2013 and May 2014 at Prince Sultan Military Medical City (PSMMC), Riyadh, Kingdom of Saudi Arabia.

**Sampling technique.** The respondents were purposively and conveniently selected and interviewed using the Arabic questionnaire including demographics, duration of diabetes mellitus, history of diabetes education, hemoglobin A1c (HbA1c), presence of lipodystrophy at insulin injection sites, diabetes treatment, frequency of DKA, reason for DKA and reason for stopping insulin.

**Inclusion and exclusion criteria.** Type 1 adolescents aged 13-18 years and Saudi nationals were included in the study, while adolescents who had a history of psychopathology, visual, hearing, or cognitive impairment, and episodes of DKA at the onset of diabetes were excluded. Adolescent treated with an insulin pump (n=1), and twice daily insulin injections (n=1) were excluded due to small numbers.

**Informed consent.** Parents and their adolescents were informed regarding the purpose and methods of the research, both verbally and in written form. Written consent was obtained from the parents and verbal consent from the adolescents before the completion of study measurement. This study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000, and the Research Ethics Committee of PSMMC approved the protocol of this study.

**Measures. Diabetic ketoacidosis.** Diabetic ketoacidosis is an episode of hyperglycemia and ketoacidosis leading to an emergency department visit and/or hospital admission. In this study, DKA is defined as: 1) blood glucose level higher than 250 mg/dL (>13 mmol/L); 2) presence of large or moderate ketone level in urine or serum; and 3) arterial blood pH level lower than 7.30, venous blood pH level lower than 7.25, or serum bicarbonate lower than 15 mEq/L.<sup>16</sup>

**Hemoglobin A1c.** The HbA1c test is the most reliable measure of glycemic control and diagnostic test

for diabetes.<sup>17</sup> During the study, the participants' most recent insulin dose and HbA1c values for the blood glucose control were taken from the medical records.

**Statistical analysis.** Data analysis was carried out using Microsoft Excel 2002 (Microsoft Corporation, Seattle, WA, USA), and the Statistical Package for Social Sciences version 16 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was performed for equal variances across the groups. In addition to the descriptive analysis, "t" test and the Tukey post-hoc test was used to look at differences among the groups. Multivariate linear regression analysis was carried out to find out the variables associated with RDKA. A *p*-value of <0.05 was considered statistically significant.

**Results.** The demographic variables of the study population are shown in Table 1. The mean age of the study cohort was 15.2±1.63 (mean ± SD) years. Fifty-seven were males (55.3%) and 46 were females (44.7%). The mean (± SD) duration of diabetes was 7.3±4.2 years, and more than 55% of the study population had T1DM for >5 years. Table 2 shows the frequency and reasons for RDKA and discontinued insulin. Majority of the patients had experienced one episode of DKA and stopped insulin, a higher percentage of adolescents gave no reason for insulin discontinuation. Table 3 shows the mean differences of RDKA frequency among the study population. The frequency of RDKA was higher in females compared to their counterpart. Compared with adolescents who had HbA1c ≤9, significant differences were found in adolescents with HbA1c >9. Similarly, adolescents who stopped insulin and those with lipodystrophy at injection site showed higher mean scores of RDKA. No significant association was found with age, gender, treatment type, history of diabetes education and duration of T1DM. Regression analysis revealed that those who had higher HbA1c level and those who had lipodystrophy were the independent risk factor for RDKA (Table 4).

**Discussion.** This study determined the frequency and associated risk factors of RDKA among Saudi adolescents with T1DM. Our results show that around 56 participants had one episode of DKA, 41 had 2 episodes, and 6 had ≥3 episodes. Studies reported that T1DM is the most frequent endocrine disease in children, with 65,000 children diagnosed worldwide every year. Up to 80% of these children, specifically early teenage years, present with DKA, which is associated with both short-term risks and long-term consequences.<sup>18,19</sup> Also, there is wide geographic difference in the incidence

of DKA rates inversely associate with the regional incidence of DKA among adolescents with T1DM. In children with established diabetes, the risk of DKA in established T1DM is 1-10% per patient per year.<sup>20-22</sup>

Several studies reported that adolescent girls were the highest risk for RDKA, which is confirmed by the present study.<sup>6,16,23</sup> This could be related to issues of body image because adolescent girls with diabetes often omit insulin injections to lose weight.<sup>24</sup> Further, girls with RDKA have also been shown to exhibit more behavioral problems, lower social competence, and higher levels of family conflict.<sup>7</sup> Many studies have addressed that omitting insulin in established T1DM is the leading and the most prevalent cause of RDKA.<sup>16,25</sup> Observational studies in urban African Americans have stated that more than one-half of DKA cases in patients with diabetes were caused by noncompliance with insulin therapy. Recently, Randall et al<sup>26</sup> also stated

**Table 1 -** Demographic variables of the study population among Saudi adolescents with type 1 diabetes mellitus (DM).

Variable(s)	Frequency	(%)
<i>Gender</i>		
Male	57	(55.3)
Female	46	(44.7)
<i>Age (years)</i>		
13-15 years	47	(45.6)
16-18 years	56	(54.4)
<i>Duration of DM (years)</i>		
1-5 years	46	(44.7)
>5 years	57	(55.3)
<i>History of diabetes education</i>		
Yes	95	(92.2)
No	8	(7.8)
<i>HbA1c</i>		
≤9	45	(43.7)
>9	58	(56.3)
<i>Lipodystrophy</i>		
No	62	(60.2)
Yes	41	(39.8)

**Table 2 -** Frequency and reasons for recurrence of RDKA and discontinued insulin among Saudi adolescents with type 1 diabetes mellitus.

Variable(s)	Frequency	(%)
<i>Frequency of recurrent ketoacidosis</i>		
One	56	(54.4)
Two	41	(39.8)
Three and more than 3	6	(5.8)
<i>Reasons for recurrent diabetic ketoacidosis</i>		
Discontinued insulin	67	(65.0)
Infectious illness	31	(30.1)
Unknown and other	5	(4.9)
<i>Reasons for discontinued insulin</i>		
Given no reason	31	(46.3)
Feeling sick	25	(37.3)
Combination of reasons	7	(10.4)
Lack of supplies and others	4	(6.0)
RDKA - recurrent diabetic ketoacidosis		

**Table 3** - Mean differences of recurrent diabetic ketoacidosis (RDKA) among the study population among Saudi adolescents with type 1 diabetes mellitus.

Variable(s)	RDKA (mean ± SD)
<b>Gender</b>	
Male	1.54±0.69
Female	1.73±0.66
<b>Age (years)</b>	
13 years-15 years	1.57±0.7
16-18 years	1.68±0.6
<b>Duration of diabetes mellitus (years)</b>	
1-5 years	1.54±0.72
>5 years	1.7±0.65
<b>History of diabetes education</b>	
No	1.38±0.51
Yes	1.47±0.32
<b>HbA1c</b>	
≤9	1.36±0.48
>9	2.32±0.53*
<b>Lipodystrophy</b>	
No	1.52±0.62
Yes	2.4±0.5*
<b>Reason for stopping insulin</b>	
Given no reason	2.50±0.54
Feeling sick	1.59±0.67#
Combination of reasons	1.63±0.68†
Lack of supplies	1.38±0.51

Values are presented as mean±standard deviation (t-test, one way analysis of variance, and Tukey post hoc test), \*≤9 HbA1c versus >9 HbA1c, \*Lipodystrophy versus no lipodystrophy, #Given no reason versus feeling sick, †Given no reason versus combination of reasons

**Table 4** - Results of multiple linear regression analysis among Saudi adolescents with type 1 diabetes mellitus.

Variable	Frequency of recurrent diabetic ketoacidosis 95%				
	β coefficients	Confidence interval		t value	P-value
>9 HbA1c	0.206	0.077	0.335	3.16	0.002
Lipodystrophy (yes)	0.768	0.407	1.12	4.222	0.001
Given no reason for RDKA	-0.008	-0.147	0.131	-0.112	0.911

RDKA - recurrent diabetic ketoacidosis

that poor adherence to insulin therapy is the leading precipitating cause of DKA and lack of adherence to insulin treatment relates to a multitude of socioeconomic and psychosocial factors. The present study results also indicate that discontinuation of insulin therapy (65%) was the major precipitating cause of RDKA followed by infection (30.1%). Further, studies reported that feeling sick is the major reason for stopping insulin among the diabetes patients.<sup>26</sup> In contrast to previous studies, we found that unknown reasons for stopping insulin was the major reason followed by sickness. Education on self-managing diabetes in order to prevent DKA, is essential to reduce the risk of developing this acute complication. Good self-monitoring and regular insulin

doses according to need are the primary preventive measures for the condition.

It has been reported by many studies that the threat of DKA is higher in adolescents with poor metabolic control or prior episodes of DKA, adolescents with psychiatric problems, including those with eating problems, children with difficult or unstable family situations,<sup>16,27</sup> and adolescents with limited access to medical services.<sup>20</sup> Further studies reported that patients with poorer glycemic control had higher risks of DKA, mainly those with HbA1c ≥10.0%.<sup>28,29</sup> In the present study, we found that adolescents with higher levels of HbA1c had higher risks of DKA. Significantly, a higher mean score of DKA was found in adolescents with lipodystrophy, which is confirmed by a previous study.<sup>30</sup> Regression analysis also showed that HbA1c level and lipodystrophy were the independent risk factors for RDKA.

The major limitations of this study include: the limited number of risk factors, limited social and demographic factors examined, a small number of adolescent examined, and performance at only a single center. More studies on a larger scale are needed to address the limitations indicated. Despite the limitations, the study delivers valuable data for RDKA among adolescents with T1DM in Saudi Arabia.

In conclusion, the frequency of RDKA was significantly greater in the T1DM adolescents with a higher HbA1c level, lipodystrophy, and those who had discontinued insulin treatment. Understanding the effect of associated risk factors of RDKA among adolescents and their families with T1DM is important for day-to-day clinical management and also for public health policy initiatives in order to improve the health outcomes of those with T1DM. Multidisciplinary, comprehensive diabetes education should be offered to control modifiable risk factors in these patients

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