Diabetic Ketoacidosis: Clinical Characteristics, Precipitating Factors and Outcomes of Care

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ABSTRACT: **Background:** Diabetic ketoacidosis (DKA) is a common and serious complication of diabetes mellitus (DM).
Objectives: To evaluate the clinical characteristics, hospital management and outcomes of patients with DKA.
Methods: We performed a retrospective cohort study of patients hospitalized with DKA during the period 1 January 2003 to 1 January 2010. Three groups were compared: patients with mild DKA, with moderate DKA, and with severe DKA. The primary outcome was in-hospital all-cause mortality. The secondary outcomes were 30 days all-cause mortality, length of hospital stay, and complication rate.
Results: The study population comprised 220 patients with DKA. In the mild (78 patients) and moderate (116 patients) groups there was a higher proportion of patients with type 1 DM (75.6%, 79.3%) compared with 57.7% in the severe group (26 patients, $P = 0.08$). HbA1c levels prior to admission were high in all three groups, without significant difference (10.9 ± 2.2, 10.7 ± 1.9, and 10.6 ± 2.4 respectively, $P = 0.9$). In all groups the most frequent precipitating factors were related to insulin therapy and infections. The patients with severe DKA had more electrolyte abnormalities (hypokalemia, hypomagnesemia, hypophosphatemia) compared with the mild and moderate forms of the disease. While 72.7% of the entire cohort was hospitalized in the general medical ward, 80.8% of those with severe DKA were admitted to the intensive care unit. The in-hospital mortality rate for the entire cohort was 4.1%, comparable with previous data from experienced centers. Advanced age, mechanical ventilation and bedridden state were independent predictors associated with 30 day mortality: hazard ratio (HR) 1.1, 95% confidence interval (CI) 1.02–1.11; HR 6.8, 95% CI 2.03–23.1; and HR 3.8, 95% CI 1.13–12.7, respectively.
Conclusions: Patients with DKA in our study were generally poorly controlled prior to their admission, as reflected by high HbA1c levels. Type 2 DM is frequently associated with DKA including the severe form of the disease. The most common precipitating factors for the development of DKA were related to insulin therapy and infections. Advanced age, mechanical ventilation and bedridden state were independent predictors of 30 day mortality.

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KEY WORDS: diabetic ketoacidosis (DKA), diabetes mellitus (DM), site of care, intensive care unit (ICU), general medical ward

Diabetic ketoacidosis is the most common and serious acute complication of diabetes. Its incidence remains high, between 4.6 and 8.0 per 1000 diabetic subjects [1,2]. DKA typically affects patients with type 1 DM, but it can sometimes complicate the course of patients with type 2 DM [3]. It has long been known that patients with type 2 DM, particularly of prolonged duration, may develop DKA under stressful conditions, such as trauma, surgery, or infections. Over the last decade the incidence of DKA in patients with atypical diabetes or ketosis-prone diabetes has increased, and the prevalence of LADA (**l**atent **a**utoimmune **d**iabetes in **a**dults) has been estimated to be as high as 10% of all type 2 diabetics [3,4]. Thus, DKA can no longer be considered pathognomonic for type 1 DM alone [3]. Most patients with autoimmune type 1 DM and DKA have either an absolute or near absolute deficiency of insulin [3,5]. However, most patients with type 2 DM who develop DKA due to stress or intercurrent illness have measurable, even increased, though relatively deficient, insulin levels [3,6]. In this group of patients with relative insulin deficiency, the metabolic decompensation results from the anti-insulin effect of counter-regulatory hormones, dehydration, and metabolic acidosis [7].

The two most common precipitating factors are infections and problems related to insulin therapy (omission of or inadequate insulin therapy, discontinuation of insulin use) [8,9]. Other, less frequent, precipitating factors include pancreatitis, myocardial infarction, stroke, trauma, and alcohol and drug abuse [9].

DKA = diabetic ketoacidosis
DM = diabetes mellitus

The optimal hospital site to manage patients with DKA (intensive care unit or general medical ward) is an important issue. To date, no randomized prospective studies have evaluated this question. Given the lack of such studies, the decision where to care for patients with DKA should be based on known clinical prognostic indicators and on the local availability of hospital resources [7,10]. The response to initial therapy in the emergency department can be used as a guideline for choosing the most appropriate hospital site for further care [7]. Admission to the ICU should be considered for patients with hypotension or oliguria refractory to initial rehydration and for patients with mental obtundation or coma [7]. Patients who are mildly ketotic and without severe systemic manifestations can be effectively managed in a general medical ward [7].

The mortality rate from DKA has sharply declined over the last few decades (3.4% to 4.6%), probably due to improved recognition and management [1,11]. DKA represents 7.6% of admissions to intensive care units and the mortality rate in these patients varies from 5% to 13% [12,13]. Clinical outcomes of DKA are much more influenced by the underlying precipitating illness, the initial biochemical data, and systemic manifestations than the metabolic complications [6,12].

The aims of our study were to evaluate the clinical characteristics, hospital management, and outcomes of patients with DKA.

PATIENTS AND METHODS

We performed a retrospective analysis of all episodes of DKA during the period 1 January 2003 to 1 January 2010 in patients admitted to the Soroka University Medical Center, a 1000 bed tertiary care teaching hospital that serves as the only tertiary referral hospital for southern Israel (Beer Sheva district, estimated population 700,000). The primary outcome was all-cause in-hospital mortality. The secondary outcomes were 30 days all-cause mortality, length of hospital stay, and complication rate. Complications included sepsis, respiratory failure, multiple organ failure, stroke, and myocardial infarction.

We used discharge diagnoses (ICD-9) to identify subjects with DKA. Diabetic ketoacidosis was defined as a triad consisting of hyperglycemia, ketosis and acidosis. We classified our patients into three groups – mild, moderate and severe – according to the revised biochemical criteria of the American Diabetic Association [3,7,9].

Diagnostic criteria for type 1 DM were exclusive insulin therapy since diagnosis and previous ketosis; and for type 2 DM, a history of metabolic control with oral hypoglycemic drugs and no previous ketosis.

ICU = intensive care unit

All patients were managed initially in the emergency department based on American Diabetes Association guidelines [7] and were then transferred to the ICU or general medical ward according to severity of the disease. All teams were experienced in the care of patients with DKA.

Demographic characteristics, ICD-9 diagnoses, medications, and clinical and laboratory data were retrieved from comprehensive chart reviews and from the hospital computerized database. All fatal cases were investigated further for better understanding of the in-hospital course and cause of death. The study was approved by the Institutional Review Board prior to its initiation.

STATISTICAL ANALYSIS

The results are presented as the mean ± standard deviation or as median and interquartile range (25th, 75th percentile) for continuous variables and as the total number of patients (percentage of total patients) for categorical data. Chi-square test was used for the comparison of categorical variables. Student's *t*-test was used for comparison of the continuous variables. Kruskal-Wallis one-way analysis of variance by ranks was used to compare the groups of sample data of variables with abnormal distribution. A two-sided P value < 0.05 was considered statistically significant. Data summaries were performed using the Statistical Package for Social Sciences (SPSS, Chicago Inc.) windows version 16.0.

For multivariable analysis, the binary logistic regression model was applied. The initial selection of the variables entered into the model was based on univariate analysis significance with inclusion criteria of $P < 0.10$. The results of multivariate analysis are presented as the hazard ratio with 95% confidence interval.

RESULTS

During the period 1 January 2003 to 1 January 2010 a total of 274 patients were admitted to our hospital with the diagnosis of DKA. Fifty-four patients were excluded from the study due to incomplete data or incorrect diagnosis of DKA according to the criteria of the American Diabetes Association.

The study cohort included 220 patients with the diagnosis of DKA. That cohort was categorized according to severity as follows: 78 patients (35.5%) had mild DKA, 116 patients (52.6%) had moderate DKA and 26 patients (11.8%) had severe DKA. Clinical characteristics of the entire cohort are shown in Table 1. The majority of the cohort patients, including those with severe DKA, were women (59.5%).

In all groups the predominant precipitating factors were related to insulin therapy (missed insulin injection, change in insulin dose or regimen, problem with insulin pump) and infections. However, the factors related to insulin therapy were more common in mild and moderate DKA; infections were more common for patients with severe DKA.

In the mild and moderate groups of patients there was a higher percentage of patients with type 1 DM compared to the group with severe DKA, although this was not statistically significant (75.6%, 79.3% and 57.7% respectively, $P = 0.08$). Type 2 DM was identified in 15.9% and new-onset DM in 8.6% of all cases. There was no difference in the number of patients with previous episodes of DKA or with new-onset DKA between the groups.

Significantly more patients with severe DKA were on oral hypoglycemic drug therapy (34.6% in the severe group compared to 11.5% and 13.8% in the mild and moderate groups respectively, $P = 0.03$).

HbA1c level was high in all the groups. No significant difference was found between the groups of patients regarding comorbidities, except that in the severe DKA group there were more bedridden patients. Patients with more severe cases of DKA had more electrolyte disturbances.

In-hospital management and clinical outcomes are shown in Table 2. Significantly more patients with severe DKA were admitted to the ICU compared to the general medical ward (80.8% vs. 19.2%, $P < 0.001$). In contrast, most of the patients in the mild and moderate groups were hospitalized in the general medical ward. Only five patients with severe DKA were hospitalized in the general medical ward. All of these patients were elderly bedridden debilitated patients in whom the intensity of care was limited by their legal guardians and next of kin.

Significantly more patients in the severe DKA group (23.1%) needed ventilatory support. The total in-hospital mortality rate of patients with DKA was 4.1%. Two fatal events (1.6%) occurred in patients with mild DKA, four (3.3%) in the moderate group and three (11.5%) in the severe group ($P = 0.041$). No death was attributable solely to the metabolic complications of DKA. Most of the fatalities (seven of nine patients) were elderly debilitated patients with several severe comorbid diseases who presented with DKA in combination with severe sepsis associated with multiple organ failure. In all the patients who eventually expired, the metabolic alterations and hyperosmolar state were successfully treated before their death. The rates of secondary outcomes (30 day all-cause mortality, length of hospital stay, complication rates) were worse in the severe group.

The list of variables included in the multivariate model were: age, DKA severity, bedridden state, steroid therapy, ischemic heart disease, chronic renal failure, DM type 2, congestive heart failure, and mechanical ventilation. Multivariate analysis of factors associated with 30 day mortality [Table 3] revealed that advanced age, mechanical ventilation and bedridden state were independent predictors (hazard ratio 1.1, 95% confidence interval 1.02–1.11; HR 6.8, 95% CI 2.03–23.1; and HR 3.8, 95% CI 1.13–12.7, respectively).

HR = hazard ratio
CI = confidence interval

Table 1. Comparison of clinical characteristics of patients with DKA

	Mild DKA n=78 (35.5%)	Moderate DKA n=116 (52.7%)	Severe DKA n=26 (11.8%)	*P* value
Age (yrs)	49.5 ± 18.4	41.5 ± 18.0	43.8 ± 20.3	0.2
Men (%)	30 (38.5)	50 (43.1)	9 (34.5)	0.6
Precipitating factors				
Problem related to insulin therapy (%)	27 (34.6)	52 (44.8)	10 (38.5)	0.5
Infections (%)	24 (30.8)	36 (31.0)	12 (46.2)	0.4
Other* (%)	7 (9.0)	7 (6.0)	None	0.08
Unknown (%)	20 (25.6)	22 (19.0)	4 (15.3)	0.4
Diabetes status				
Type1 DM (%)	59 (75.6)	92 (79.3)	15 (57.7)	0.08
Type 2 DM (%)	11 (14.1)	15 (12.9)	9 (34.6)	0.02
New-onset DM (%)	8 (10.3)	9 (7.8)	2 (7.7)	0.8
DKA in the past (%)	37 (47.4)	70 (60.3)	14 (56.0)	0.1
Insulin therapy (%)	64 (82.1)	101 (87.1)	18 (69.2)	0.08
Oral hypoglycemic drug therapy (%)	9 (11.5)	16 (13.8)	9 (34.6)	0.03
HbA1c (%)	10.6 ± 2.4	10.7 ± 1.9	10.9 ± 2.2	0.9
Baseline comorbidities				
Ischemic heart disease (%)	7 (9.0)	17 (14.7)	6 (23.1)	0.1
Chronic heart failure (%)	3 (3.8)	7 (6.0)	2 (7.7)	0.7
Chronic obstructive lung disease (%)	1 (1.3)	1(0.9)	2 (7.7)	0.5
Chronic renal failure (%)	7 (9.0)	10 (8.6)	2 (7.7)	0.9
Bedridden (%)	9 (11.5)	3 (2.6)	3 (11.5)	0.03
Steroid therapy (%)	2 (2.6)	4 (3.4)	1 (3.8)	0.9
Admission laboratory tests				
Plasma glucose (mg/dl)	495 ± 212	576 ± 181	706 ± 217	< 0.001
Urea (mg/dl)	60 ± 49	62 ± 35	72 ± 49	0.2
Creatinine (mg/dl)	1.13 ± 0.6	1.28 ± 0.9	1.42 ± 0.8	0.045
Elevated troponin (> 0.03 ng/ml)	4 (5.1)	9 (7.8)	4 (15.4)	0.6
White blood cells (x 10^3/ul)	14.3 ± 5.8	14.8 ± 6.5	22.6 ± 10.2	< 0.001
Hemoglobin (g/dl)	13.8 ± 1.9	14.2 ± 1.9	13.1 ± 2.9	0.028
Systolic blood pressure (mmHg)	129 ± 24	125 ± 24	129 ± 38	0.7
Hypokalemia (< 3.5 mEq/L) (%)	20 (26.5)	46 (39.6)	18 (69.2)	< 0.001
Hypomagnesemia (< 1.6 mg/dl) (%)	19 (24.4)	30 (25.9)	12 (46.2)	0.1
Hypophosphatemia (< 2.5 mg/dl) (%)	40 (51.3)	76 (65.5)	22 (84.6)	0.01

Values are mean ± SD

*Other: myocardial infarction, psychiatric drugs, alcohol intoxication, biliary colic, surgery, peptic disease, suicide attempt, pregnancy and delivery

Table 2. In-hospital management and clinical outcomes

Outcome	Mild DKA (n=78)	Moderate DKA (n=116)	Severe DKA (n=26)	*P* value
Admission to ICU (%)	7 (9.0)	32 (27.6)	21 (80.8)	< 0.001
Mechanical ventilation (%)	none	2 (1.7)	6 (23.1)	< 0.001
Length of hospital stay (days) median (interquartile range)	3 (2;5)	3 (2; 5)	6 (3.12)	0.01
Total complication rate (%)*	2 (2.6)	5 (4.3)	7 (26.9)	0.001
In-hospital mortality (%)	2 (2.6)	4 (3.4)	3 (11.5)	0.1
30 day mortality (%)	3 (3.8)	5 (4.3)	4 (15.4)	0.06

* Complications included sepsis, respiratory failure, multiple organ failure, stroke and myocardial infarction

DISCUSSION

In the present study the most common precipitating factors for the development of DKA were related to insulin therapy

Table 3. Multivariate analysis of factors associated with 30 day mortality

	Hazard ratio	95% confidence interval	*P* value
Age	1.1	1.02–1.11	0.007
Mechanical ventilation	6.8	2.03–23.1	0.002
Bedridden	3.8	1.13–12.7	0.03

The list of variables included in the multivariate model are: age, DKA severity, bedridden state, steroid therapy, ischemic heart disease, chronic renal failure, DM type 2, congestive hart failure, mechanical ventilation

(e.g., missed insulin injection, change in insulin dose or regimen, problem with insulin pump) and infections. While in the mild and moderate groups the most common precipitating factor was related to insulin, in the severe group infections were the most common precipitating factor. In our study there was a higher percentage of insulin-related precipitating factors than in previous studies performed in developed countries where the most common factor was related to concurrent infection [8,9,14].

New-onset DM was identified in 8.6% of all DKA cases, whereas previous studies reported a rate of 20–30% [1]. This difference may be attributable to better identification of new-onset DM by primary care providers and improved screening procedures that have been widely adopted in the last decade in Israel [15-18]. In this study 15.9% of patients had type 2 DM. In other studies the prevalence of patients with type 2 DM in DKA ranged from 12% to 56% [3,5,13,19].

Most of the patients with DKA were poorly controlled, as reflected by the high HbA1c levels. HbA1c may be useful in determining whether the acute episode is the expression of previously undiagnosed or poorly controlled diabetes, or a truly acute deviation in an otherwise well-controlled patient [5]. Chronic hyperglycemia has been shown to be associated with decreased insulin secretion [3,19,20] and with impaired glucose disposal in peripheral tissues [3]. This chronic "glucose toxicity" has important implications for both the pathogenesis and management of acute hyperglycemic crises. The poor metabolic control of most of our DKA cohort suggests that this group requires particular attention to prevent recurrence of DKA. It stands to reason, but remains to be proven, that more aggressive therapy of DM or earlier introduction of insulin therapy in these patients will decrease the risk for development of DKA.

Most of the patients with severe DKA in our study were hospitalized in the ICU, and most patients with mild and moderate forms of DKA were hospitalized in the general medical ward and had favorable outcomes.

In the present study the in-hospital mortality of patients with DKA was 4.1%, consistent with previous data from experienced centers [21,22]. According to the literature, the most powerful predictor of mortality in patients with DKA is the age of the patient [8,9,21,22]. Other predictors of mortality are coma and hypotension [8], concurrent serious illness (such as infection, hepatic failure, gastrointestinal bleeding or cancer) [23], and altered mental status [24]. In the present study multivariate analysis of factors associated with 30 day mortality revealed that advanced age, mechanical ventilation and bedridden state were independent predictors of 30 day mortality. These data corroborate the previous literature and confirm the effect of age and general condition of the patient on outcomes of DKA.

STUDY LIMITATIONS

Our study has several limitations. It was retrospective and performed at one institution, and we did not analyze the differences in insulin types and types of oral glucose-lowering agents that patients received before hospitalization. HbA1c level was not available for all patients. Lactate level was measured only in a few patients hospitalized in the ICU, which theoretically could contribute to a bias by including patients with acidosis related to other conditions even if they fulfilled the criteria for DKA.

CONCLUSIONS

Patients with DKA in our study were generally poorly controlled prior to their admission, as reflected by high HbA1c levels. Type 2 DM is frequently associated with DKA, including the severe form of the disease. The most common precipitating factors for the development of DKA were related to insulin therapy and infections. Advanced age, mechanical ventilation and bedridden state were independent predictors of 30 day mortality.

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