Clinical And Laboratory Characteristics Of Diabetic Ketoacidosis In Adult Diabetic Patients

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Citation

Abstract
Objectives: Aim of this study was to record the epidemiological, clinical and biochemical features of DKA and their prognostic significance in adult diabetics.

Patients and methods: The medical records of patients admitted due to DKA, between 2001 and 2006, were retrospectively reviewed. The patients were classified as type 1, type 2, based mainly on treatment history and autoantibody status, with c-peptide measurement for newly diagnosed patients.

Results: Of 56 patients (19 male, 37 females) with mean average of age 63.6 years, 30(53.5%) had type 2 diabetes, 16(28.5%) had type 1 diabetes and 10 (18%) were newly diagnosed diabetics. In 32.2% of patients the precipitating factor of DKA was an acute infection, with most frequent urinary tract infections (50%). Potassium concentrations found to be abnormal in 42.8% of patients and 10.7% had hypokalemia in admission. The duration of hospitalization was 10±7.6 days. Type 1 DM group was more acidic than Type 2 DM group (arterial pH, 7.16±0.18 vs 7.22±0.13, p=0.01). In hospital mortality (12.5%) was significantly correlated with increased age (p<0.01).

Conclusion: DKA occurs in a relatively high proportion in individuals with type 2 diabetes. The most frequent cause of DKA is acute infection. Advanced age is associated with an increased risk of mortality.

INTRODUCTION
Diabetic ketoacidosis (DKA) is a serious complication of diabetes mellitus (DM), characterised by the biochemical triad of hyperglycemia, ketonemia and acidosis (1, 2). As traditional teaching describes, DKA is typical of Type 1 DM, lately called insulin depended diabetes mellitus (IDDM). More recently, there have been multiple reports of DKA in patients with type 2 diabetes mellitus, previously called non-insulin depended diabetes mellitus (NIDDM) (3,4,5).

The annual incidence rate for DKA, estimated for population-based studies ranges from 4.6 to 8 cases per 1000 patients with diabetes (6,7,8), while DKA as initial presentation of disease accounts for almost 3% of type 1 diabetic patients (9). In the US hospitalizations for DKA have been seriously increased during the past 20 years (9). Part of this increased frequency of admissions may be associated to the increased prevalence of type 2 diabetes.

The aim of this study was to review the clinical characteristics and outcomes of DKA among the Greek population. This report includes epidemiological, clinical and biochemical features on admissions, the mortality rates and prognostic factors associated with outcome.

MATERIALS AND METHODS
The patient population included in this study was adult diabetic victims (age > 18 years, European descent) who had been admitted to the division of Internal Medicine, Konstantopoulio, General Hospital “Agia Olga” of Nea Ionia, due to DKA, from 2000 to 2005. All information was obtained retrospectively by patients' medical records.

DKA was defined in emergency department by the presence of 3 laboratory findings: a plasma glucose level of 250 mg/dl or higher, a serum bicarbonate level of 15 mEq/L or lower or
arterial pH<7.3 and moderate or large urinary (>++) or blood ketones (>3mmol/l). The therapeutic management of DKA included intravenous insulin administration, hydration and electrolyte replacement according to the American Diabetes Association practice guidelines. Fluid administration was usually in the form of normal saline at 1 L/h, then 1 L/2 h with a further 1 L/4–8 h. A dextrose containing fluid was initiated when the plasma glucose level fell below 15 mmol/L. Fluid management was individualized according to the hydration status and electrolyte abnormalities. If there was evidence of hypotension, patients were usually treated with colloid solutions and if severe hypernatraemia was present, intravenous fluids were administered in the form of hypotonic (0.45%) saline. Insulin was usually given as a 5–10 IU i.v. bolus and then by infusion at 1–6 IU/h. The insulin-infusion rate was adjusted according to hourly venous or capillary glucose assessment. Potassium replacement was started only if [K+] <4 mEq/l and did not generally exceed 40mEq/l in first hour IV until plasma potassium raised over 4.5 mEq/l. Precipitating factors were immediately recognised and treated vigorously. This protocol was begun as soon as possible after preliminary evaluation in the emergency department.

Initial investigations included capillary and serum glucose measurement, serum electrolytes, full blood examination, arterial blood gases, urinalysis, chest radiograph and electrocardiogram (ECG). Epidemiological data were collected and parameters such as age, gender, prominent symptom at presentation, precipitating causes of DKA, type of DM, length of hospitalization and final outcome were analysed.

Individuals under insulin treatment and a prior history of DKA were classified as Type 1 DM. Patients managed at some point with diet or an oral agent and no prior history of DKA were classified as Type 2 DM. None of the DKA-onset diabetes patients had phenotypic features of type 2 diabetes (such as obesity, acanthosis nigricans, or a family history of type 2 diabetes) and all were tested for autoimmune antibody. Patients who had no prior history of diabetes undertook a c-peptide test (fasting as well as a second measurement 6min after iv injection of 1 mg glucagon) and were classified as type 1 diabetic patients if they had typical clinical and laboratory characteristics of type 1 DM and a very low fasting c-peptide (0.0-0.17 ng/ml) which was not altered significantly after stimulation with glucagon (0.0-0.29 ng/ml).

Statistical analysis was performed by means of Student’s t-test, and the χ2 test as appropriate. A regression analysis was accomplished to determine the main predictors of death (7 cases) in the study population.

RESULTS

During the study period, 56 patients achieved the diagnostic criteria of DKA and were included in this analysis. Nineteen were male and thirty-seven were female. The mean age at the time of the episode of DKA was 63.13 years (between 20 and 89 years). A synopsis of epidemiological data for the subgroups analyzed is presented in Table 1. 18.2% were newly diagnosed DM and DKA was the initial manifestation of disease, 53.3% were classified as type 2 DM and 28.5% as type 1 DM. Symptoms recognized to be present at the time of presentation are summarized in Table 2.

**Figure 1**

Table 1: Epidemiological data for subgroups of patients classified by type of DM

<table>
<thead>
<tr>
<th>Type 1 DM</th>
<th>Type 2 DM</th>
<th>Newly Diagnosed DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td>Age Mean (SD)</td>
<td>55.6 ± 24.6</td>
<td>69.9 ± 14.3</td>
</tr>
<tr>
<td>Male</td>
<td>8(50%)</td>
<td>9(30%)</td>
</tr>
<tr>
<td>Female</td>
<td>8(50%)</td>
<td>22(70%)</td>
</tr>
</tbody>
</table>

**Figure 2**

Table 2: Frequency of prominent symptom of patients admitted with moderate to severe DKA

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>25</td>
</tr>
<tr>
<td>Alteration in sensoria</td>
<td>23.2</td>
</tr>
<tr>
<td>Fever</td>
<td>9</td>
</tr>
<tr>
<td>Polyuria</td>
<td>9</td>
</tr>
<tr>
<td>Polydipsia</td>
<td>7.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7.1</td>
</tr>
<tr>
<td>Decompensated DM</td>
<td>7.1</td>
</tr>
</tbody>
</table>

A possible cause for the development of DKA was identified in 75% of patients (Table 3). 10 out of 56 patients were newly diagnosed diabetics. Thirty two percent of patients suffered from infection (25%, Type 1 DM and 35%, Type 2
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DM) including urinary tract infections (50%), upper respiratory tract infection, pneumonia and lower limb gangrene (one patient). Insulin withdrawal was implicated in 8% of admissions, while systemic disease (cerebrovascular attack, respiratory disease) (12%) was an additional precipitating factor. In 25% of cases (37.5%, Type 1 DM and in 33.3% of patients with Type 2 DM) the cause of DKA was unknown. Cardiological problems concerned primarily cardiac failure and atypical chest pain, but not acute myocardial infarction, which was treated in the cardiology department and was excluded as a cause of DKA in this study.

Figure 3
Table 3: Causes of DKA in patients with DM

Table 4 provides a summary of the distribution of various laboratory values on admission. Mean blood glucose values differed significantly among newly diagnosed (714.2 ± 339.6 mg/dL, p<0.05) and the other two study groups of patients (524.375 ± 219.8 mg/Dl, type 2 and 510.28 ± 186.69 type 2). The mean pH value of plasma in type 2 group was significantly higher than that of type 1 group (7.22±0.13 vs 7.16±0.18 p<0.05).

Potassium concentration was between normal ranges on admission in 52.5% of patients, while 36.5% and 14%, and suffered from hyperkalemia and hypokalemia respectively. There was recorded no statistically significant difference concerning serum potassium levels among the examined groups.

Severe DKA was found in 41% of patients, while 34% were of modest severity and 25% presented mild DKA. Patients with hyperkalemia compared with patients of normal or low potassium levels, at the time of presentation, had more severe acidosis (Table 5). They also had lower plasma glucose levels, lower serum sodium levels, lower ph values, and higher blood urea nitrogen and creatinine levels. The high-density lipoprotein cholesterol levels were similar in all groups except total cholesterol levels and triglycerides which was lower in patients with a history of type 2 diabetes than in those with type 1 diabetes (184.1± 76 mg/dL , 157.7±100.1 mg/dL vs 210.65 ± 40.85 mg/dL , 171.25± 64.76 mg/dL, respectively) and in those who were newly diagnosed diabetics (263,480±113,24, 353,23±50,36 mg/dL p=0.01).
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Age at presentation for Type 1 patients was significantly (p<0.01) less than Type 2 patients, but it was not significantly (p=0.56) less than newly diagnosed patients. In multivariate analysis (severity of DKA, glucose levels on admission, sex, duration of the disease, levels of ketones in the urine, duration of hospitalisation as dependent variables) only age was the key predictor for increased risk of death (p<0.01).

DISCUSSION

Diabetes has been classified on the basis of specific clinical and laboratory features, into two major types: type 1 diabetes formerly called juvenile-onset or insulin-dependence diabetes mellitus and type 2 diabetes, formerly called maturity-onset or non-insulin-dependence diabetes mellitus (12). Type 1 diabetes results from a cellular-mediated immune destruction of β-cells of the pancreas (13). Type 2 diabetes mellitus describes mainly individuals with insulin resistance with relative insulin deficiency (14, 15). DKA has been reported to be the first manifestation of disease especially in children and adolescents with type 1 DM (16). Type 1 diabetes results from a cellular-mediated immune destruction of β-cells of the pancreas (16). Type 2 diabetes mellitus describes mainly individuals with insulin resistance with relative insulin deficiency (14, 15). In Type 1 DM there is a tendency to ketosis, whereas in Type 2 DM occurs when there is a substantial loss of β-cell function such that the patient needs long-term insulin administration (17).

Our observations confirm that DKA can occur in patients with type 2 DM as well. Patients with DKA and a previous history of disease accounted 53% of the study population. Also it was found that patients with Type 2 diabetes had different laboratory values in admission with less severe DKA and a tendency for normal plasma potassium levels comparing with patients with type 1 DM (Table 5).

Patients with newly diagnosed DM, who present with DKA in emergency room also have different biochemical values from those with known history of diabetes (18, 19) (Table 4). These patients are seriously dehydrated (elevated values of BUN and creatinine) and appear to show more severe hyperglycemia.

As it was shown in our study up to 25% of DKA had an unidentified precipitating event (1). Commonly recognized precipitating factors include illnesses such as infections, inadequate therapy or treatment discontinuation and newly diagnosed diabetes (17, 18). Psychological matters and non-compliance are also known to be significant factors, especially in patients with recurring episodes of DKA. Infections are reported to account for nearly 30% to 40% of DKA and may be the most frequent precipitant of DKA in white populations (19, 20). In our series 8% of patients reported omission of insulin and it was attributed to a combination of reasons, not potentially identified from medical records. The majority of patients reported various causes, such as financial discomfort and fear of hypoglycemia.

The clinical presentation of DKA involves symptoms of hyperglycemia (polyuria, polydipsia, weight loss) and symptoms linked to ketonemia (vomiting, fatigue, abdominal pain, and nausea). From data in the present study derives that people with vomiting and abdominal pain visit doctor more frequently than patients with symptoms of osmotic diuresis (Table 2). The classic symptoms of DKA may not always be apparent.

The laboratory findings from our series of patients presented in Tables 4 are following the pattern expected in DKA. There are severe derangements of water and electrolytes, as a result of insulin deficiency, hyperglycemia and ketonemia. Volume depletion due to osmotic diuresis and glycosuria results in marked hyperglycemia, mild dehydration and an increase in BUN and creatinine. The metabolic acidosis in DKA develops as an answer to the increased plasma levels of metabolic acids such as acetoacetic acid and β-hydroxybutyric acid.

Even though serum sodium values might be expected to be raised in a dehydrated status, as a consequence of water loss and hyperglycemia, there is a sift of water out of cells which tends to reduce sodium concentration (21). Potassium seems to be high because of insulin deficiency, metabolic acidosis and hyperosmolality, but it is widely known that potassium is depleted in DKA (22). Interestingly, only 12% of our patients needed potassium replacement during managing their DKA.

Data analysis shows that patients with type 2 DM present moderate to severe DKA and 6% of them develop hypokalemia compared to 13% of patients with type 1 DM and hypokalemia. This finding indicates failure of insulin activity to prevent DKA. However the result of a smaller number of patients with hypokalemia in type 2 DM group underlines that insulin, which is strong regulator of
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potassium plasma concentration, exist in amounts enough to impede the course of disease, but not enough to cause hypokalemia.

The patients with newly diagnosed DM had severe DKA and a higher proportion of electrolytic disorders compared with patients of type 2 DM groups. Furthermore newly diagnosed diabetics were severely dehydrated (increased BUN and creatinine) and in their vast majority were younger than patients with type 2 DM but older than patients with type 1 DM. Patients with newly diagnosed diabetes have a more intact counterregulatory hormone system than patients with a history of diabetes, which can eventually provoke extensive ketogenesis and a more severe picture of DKA.

Hyperkalemia was expected in both groups of individuals, since the insulin deficiency was present in both and it was found greater in the more acidic group (Table 5). The normokalemia in the newly diagnosed group implies that a different mechanism, possibly associated with osmolarity, may be implicated.

The duration of treatment to hospital discharge was similar among the 3 groups (10±6 days type 1, 9.4±7 days type 2, 9.6±8 newly diagnosed). However, a more extensive time period from emergency department examination to negative urine ketones analysis for patients with type 2 DM was reported. A plausible explanation for this delay may be the difficulty to evaluate promptly patients with atypical clinical presentation.

A mortality rate of 12% found in our study is relatively high compared with other centers (23,24,25). Age was the only independent predictor of mortality in a multivariable analysis (P < 0.01). No death was attributable solely to the metabolic derangement of acidosis. The most common causes were urinary sepsis followed by pneumonia. Three of our patients needed delivery in Intensive Care Unit, due to irreversible severe metabolic acidosis.

In last decades the financial cost of DKA has been increased according recent studies in US (26,27). The efforts of medical associations and health care organizations should focused on prevention of DKA. Educational programs for patients should provide instructions for use of short acting insulin and specific diet in case of an acute illness. Patients must understand that omission of insulin treatment is life-threatening and they should seek for a professional opinion early in the course of disease. All these entail that there is always available a health care provider who will guide the patient and his family properly.

CONCLUSION

Diabetic ketoacidosis is a medical emergency that requires prompt recognition. The first approach to the patients who presents with DKA consists of a careful history and physical examination. The initial laboratory evaluation should include blood glucose, blood urea nitrogen, serum electrolytes, creatinine, osmolality, ketones, urinalysis and a complete blood count (c,). Treatment should aim to 1) restore circulatory volume and impaired electrolyte balance 2) start insulin infusion at once to restrain hyperglycemia 3) diagnosis and treatment of the possible cause which induced the development of DKA.

It appears that DKA is an expression of type 2 DM with most common cause acute infection. As it is indicated from our study prognosis is not always favorable. Mortality is increased by aging and the presence of concomitant life-threatening diseases.

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