Diabetic Ketoacidosis: Comparisons of Patient Characteristics, Clinical Presentations and Outcomes Today and 20 Years Ago

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Background: The aim of this study was to compare the clinical manifestations and outcomes of patients with diabetic ketoacidosis (DKA) today and 20 years ago.

Methods: A retrospective review was conducted of patients with DKA treated at our hospital from January 2001 through June 2002. The medical records were analyzed to identify clinical presentations, contributory factors, laboratory data, and outcomes. Additionally, data were compared with the records of patients with DKA in 1981 and 1982 at the same hospital.

Results: Data on 132 patients with 148 DKA episodes were included in the present study. When compared with the data from 20 years ago, clinical presentations, precipitating factors and laboratory data were similar. However, the mortality rate markedly decreased from 7.96% to 0.67%. Among patients with documented bacterial infections, a significantly high prevalence (70%) of *Klebsiella pneumoniae* infection was discovered. In patients with recurrent DKA, young women with type 1 diabetes accounted for most of the cases (67%) due to the omission of insulin. Eleven of 49 patients (22%) with newly diagnosed diabetes presenting with DKA were not insulin dependent during the 1.5-year follow up.

Conclusions: After 20 years, the clinical presentations and precipitating factors of DKA were similar. However, the mortality rate was significantly reduced. *Klebsiella pneumoniae* was the leading cause of bacterial infections precipitating DKA in our hospital. Young women with type 1 diabetes were at high risk of repeat DKA.

(Chang Gung Med J 2005;28:24-30)

Key words: type 1 diabetes, diabetic ketoacidosis, *Klebsiella pneumoniae*.

Diabetic ketoacidosis (DKA) is one of the most serious acute complications of diabetes. The annual incidence of DKA is about 4.6~8 episodes/1000 diabetic patients.[1] DKA also poses a huge economic burden on the medical system.[2] After the discovery of insulin in the 1920s, the mortality rate of DKA dropped, reaching 5%-15% recently. However, the mortality rate substantially increases with age and the presence of concomitant illnesses.[3,4] DKA is precipitated by an absolute or relative lack of insulin in combination with an increase in catabolic hormones, which leads to increased production of ketone bodies and glucose in the liver.[5] It is considered to arise mainly in patients

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Received: Jan. 4, 2004; Accepted: Nov. 15, 2004
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with type 1 diabetes, but it has been increasingly reported in obese patients with newly diagnosed diabetes who were subsequently insulin independent.[6-13]

We conducted a retrospective study to identify the patient characteristics, clinical manifestations, precipitating factors, laboratory data, and outcomes of DKA treatment at the Chang Gung Memorial Hospital in Linkou, Taiwan. The present data were also compared with the results of a previous report in 1985 at the same hospital.[14]

METHODS

We reviewed medical records of all patients who were admitted under the impression of DKA from January 1, 2001 through June 30, 2002 at our hospital. Patients were included in the study if they fulfilled all of the following criteria: serum sugar > 250 mg/dl (enzymatic method), serum bicarbonate concentration < 18 mmol/l, arterial pH < 7.30 (selective ion exchange method), and positive serum ketones with a ≥ 2-fold dilution by the nitroprusside reaction method with the Gluketur Test® (Roche diagnostics GmbH, Germany).[15] C-peptide level was detected using chemiluminescent immunoassay or radioimmunoassay.

The medical records were reviewed in detail including patient characteristics, initial manifestations, precipitating factors, laboratory data, treatment course, and outcome of DKA for each patient and each admission.

Culture-proven bacterial infections were defined as follows. Urinary tract infection (UTI) was diagnosed when urinary tract infection symptoms, pyuria and urine or blood culture positive for bacteria were found. Lung infection was diagnosed when respiratory infection symptoms (productive cough), significant findings on a sputum smear (neutrophils > 25/ low power field and epithelial cells <25/ low power field) and sputum or blood culture positive for bacteria were found. Skin infection was diagnosed when cutaneous infection symptoms/signs with significant blood or wound culture were found. Acute otitis externa (AOE) was diagnosed when acoustic channel discharge and culture positive for bacteria were found. Septicemia with no known focus was diagnosed when positive culture in both of two subsequent blood samples from different sites or only one positive culture with significant bacteria, e.g., gram-negative bacilli without a definite infectious focus found clinically.

Data from DKA patients 20 years ago at the same hospital,[14] including patient characteristics, initial clinical manifestations, precipitating factors, laboratory data on admission, and outcomes were compared with the present data.

The statistical analysis of demography and initial laboratory data of DKA patients were expressed as the mean ±SD.

RESULTS

The data for 132 patients with 148 episodes of DKA who visited our hospital from January 1, 2001 through June 30, 2002 were included in the study. When we compared the data with the result of the previous study, the females to males ratios were 74:58 and 49:31 in the present and previous studies, respectively, and the female patients were slightly predominant in both studies. Although patients younger than 16 years were excluded from the previous study, older patients (≥ 40 years) accounted for about 40% in both studies. The initial presentations in the present study were predominantly gastrointestinal symptoms (nausea, vomiting, abdominal pain) and dyspnea, which were consistent with the findings in the previous study. However, constitutional symptoms seemed more prevalent in the present study (Table 1). In the present study, the most common contributing factor for DKA was infection (31.7%), followed by omission of anti-diabetes drugs (27.7%), newly diagnosed diabetes (18.2%), unknown causes (16.2%) and other medical conditions (6.0%), which was similar to the previous study. However, severe co-morbid diseases seemed more prevalent in the previous study (the incidences of bacterial infection were 15.5% and 24.8%, cerebrovascular accident 0.7% and 2.7%, malignancy 0.7% and 1.7%, upper gastrointestinal bleeding 1.4% and 0.8%, and acute pancreatitis 1.4% and 0% in the present and previous studies, respectively, Table 1). The laboratory data on admissions are shown in Table 2. The degree of metabolic derangement was similar in both studies. In the previous study, a total of nine patients died of CVA (n = 3), sepsis (n = 3), malignancy (n = 2), and sudden death (n = 1). Only one patient died of pneumonia due to *Klebsiella pneumoniae* in the present study. The

Table 1. Clinical Presentations and Precipitating Factors of Patients with DKA in the Present and Previous Study

	Present study No. (%)	Previous study No. (%)
Manifestations		
Nausea/vomiting	69 (47)	74 (56)
Constitutional symptoms*	52 (35)	21 (16)
Dyspnea	43 (29)	46 (35)
Polyuria/polydipsia	36 (24)	37 (28)
Abdominal pain	36 (24)	26 (20)
Dizziness	15 (10)	15 (11)
Weight loss	15 (10)	NA
Others presentations	9 (6)†	30 (23)‡
Precipitating factors		
Infection	47 (31.7)	34 (30.1)
Bacteria	23 (15.5)	28 (24.8)
Virus	23 (15.5)	5 (4.5)
TB	1 (0.7)	1 (0.8)
Omission of anti-diabetes drug	41 (27.7)	29 (25.7)
Newly diagnosed diabetes	27 (18.2)	19 (16.8)
Unknown	24 (16.2)	22 (19.4)
CVA	1 (0.7)	3 (2.7)
Malignancy	1 (0.7)	2 (1.7)
Upper gastrointestinal bleeding	2 (1.4)	1 (0.8)
Acute pancreatitis	2 (1.4)	0
Steroid use	2 (1.4)	0
Gouty arthritis	1 (0.7)	0
Hyperthyroidism	0	1 (0.8)
Trauma	0	1 (0.8)
Pregnancy	0	1 (0.8)

Abbreviations: DKA: diabetic ketoacidosis; NA: not available.
* includes drowsy, weak, somnolence, malaise and poor appetite.
† ncludes chest pain, headaches, palpitations and sore throat.
‡ detailed presentations are not mentioned.

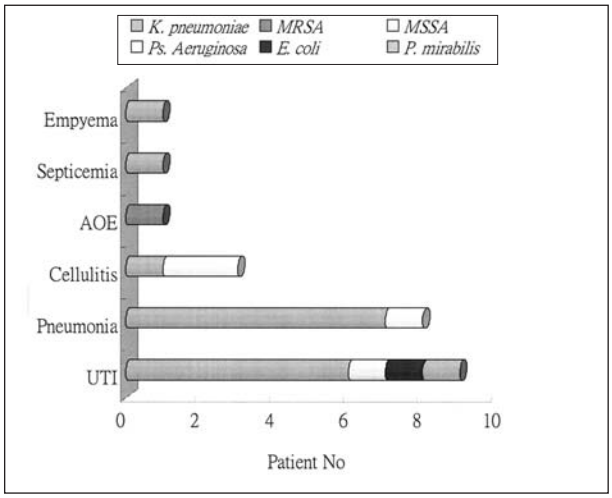

Fig. 1 Source of bacterial infections and bacterial strains in Patients with DKA. *K. pneumoniae: Klebsiella pneumoniae;* MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-susceptible *Staphylococcus aureus*; *Ps. Aeruginosa: Pseudomonas aeruginosa; E. coli: Escherichia coli; P. mirabilis: Proteus mirabilis;* AOE: acute otitis externa; UTI: urinary tract infection.

Table 2. Laboratory Data of Patients with DKA on Initial Presentation in the Present and Previous Study

	Present Study	Previous Study*
Sugar (mg/dl)	609 ±297	534
Osmolality (mOsm/kg)	326 ±28	323
Cr (mg/dl)	1.38 ±0.73	NA
Na (mEq/l)	136.4 ±7.6	135.5
K (mEq/l)	4.6 ±1.0	5.1
pH	7.13 ±0.11	7.10
HCO_3- (mmol/l)	6.0 ±3.9	6.4
WBC (x 10^3/ μl)	15.7 ±7.8	17.8

Abbreviations: DKA: diabetic ketoacidosis; NA: not available; HCO_3-: bicarbonate; WBC: white blood cell.
* reference 14

mean age of the patients who died was 57.4 years in the previous study. The only patient who died in the present study was 42 years old. The mortality rate markedly decreased from 7.96% to 0.67% after 20 years.

Among the 148 episodes of DKA in the present study, 15.5% (n = 23) of the patients had culture-proved bacterial infections (Fig. 1), and 35.2% (n = 52) of the patients received empiric antibiotics with negative bacterial cultures in suggested infection sites or blood. In addition, 49.3% (n = 73) of the patients lacked bacterial infection manifestations and did not receive antibiotics. Among those with bacterial infections, the urinary tract was the most common site (n = 9), followed by the lungs (n = 8), skin (n = 3), external acoustic channel (n = 1), and empyema (n = 1). There was one case of septicemia with an unknown focus. Notably, *Klebsiella pneumoniae* was the leading and it accounted for 70% (n = 16) of bacterial infections. Other pathogens included methicillin-susceptible *Staphylococcus aureus* (13%), methicillin-resistant *Staphylococcus aureus* (4.3%), *Escherichia coli* (4.3%), *Proteus mirabilis* (4.3%),

and *Pseudomonas aeruginosa* (4.3%). In addition to culture-proven bacterial infections, one patient had proven pulmonary tuberculosis, 21 patients had symptoms of upper respiratory tract infections and two subjects had acute gastroenteritis presentations.

Nine patients with 25 episodes of recurrent DKA were noted in the study (Table 3). All of these subjects were under insulin therapy previously and were considered as having type 1 diabetes. The gender ratio was female predominant (with a female to male ratio of 7:2), and the majority of the patients were approximately 18~27 years old. One 18-year-old woman (patient 2), who was afraid of insulin injections, had as many as seven recurrences of DKA during the 1.5-year study period. The leading precipitating cause of recurrent DKA in these nine cases, in contrast to the general data presented above, was omission of insulin (52%), infection (24%) and unknown causes (24%).

Forty-nine patients had no previous history of diabetes but developed DKA as their first diabetic presentation. Eleven of the 49 patients discontinued insulin based on clinical judgments during the subsequent follow up of more than 1.5 years. In this group, the mean age was 43.1±14.9 years, mean BMI was 27.2±5.1 kg/m^2, and mean fasting C-peptide was 2.50±5.1 ng/ml which were investigated when the clinical condition had stabilized.

Table 3. Clinical Data of Nine Patients Who Experienced Recurrent DKA

Patient No.	Gender	Age (years)	History of diabetes (years)	Total DKA episodes	Precipitating factors/ DKA episodes
1	F	10	1	2	Omission of insulin (2)
2	F	18	2	7	Omission of insulin (6)
					Infection (1)
3	F	21	7	3	Omission of insulin (1)
					Infection (2)
4	F	22	2	2	Omission of insulin (1)
					Unknown (1)
5	F	22	5	2	Infection (1)
					Unknown (1)
6	F	27	3	2	Omission of insulin (1)
					Unknown (1)
7	F	41	2	2	Omission of insulin (2)
8	M	16	2	2	Infection (2)
9	M	25	1	3	Unknown (3)

Abbreviation: DKA: diabetic ketoacidosis.

DISCUSSION

The gender, precipitating factors, clinical presentations and laboratory data were similar in the DKA patients in the present and previous studies. The severity of DKA, defined by metabolic derangement on admission (Table 2), seemed similar in both studies. Severe co-morbid diseases were more prevalent in the previous study. The treatment strategies for DKA were similar in both studies. The treatment included low dose insulin infusion (0.1-0.15 μ/kg/hr), adequate fluid and potassium supplementation, close monitoring of blood glucose and electrolytes, and treatment of precipitating factors. There were no treatment-related deaths in either study.

The mortality rate markedly decreased from 7.9% to 0.67% after 20 years. Younger patients (< 16 years) were excluded in the previous study, however, the mortality rate was 0.86% (1/116 cases) in patients older than 16 years old in present study. Similar proportions of older patients (≥ 40 years) were included in both studies. Therefore, the lower mean age of patients in the present study may not explain the lower mortality rate in the present study. In both studies, most of the patients who died had severe co-morbid disease. According to these findings, the differences in the mortality rates between the two studies may have been partly due to the concomitant life-threatening diseases. Whether advances in supportive care contributed to better outcomes in the present study is uncertain.

According to the current data, the leading cause of DKA was infectious diseases (32%). The causes of infectious disease which contributed to DKA included bacteria (49%), viruses (49%), and tuberculosis (2%). The urinary tract and lung were the most common foci of bacterial infections. Of note, among our DKA patients, *Klebsiella pneumoniae* accounted for the majority of bacterial infections. It is believed that there is no strong evidence linking diabetes mellitus and increased susceptibility to infection; however, diabetic patients are susceptible to specific infectious pathogens.[16] *Klebsiella pneumoniae* has been discovered to be a leading pathogen among diabetic patients in Taiwan for infections such as liver abscess,[17,18] empyema,[19] meningitis,[20] endophthalmitis,[21] and septicemia,[22,23]. Interestingly, our data further demonstrated *Klebsiella pneumoniae* infection played a major role in contributing to

DKA. The reason for the high prevalence in Taiwan is unknown. Further studies on leukocyte adherence, chemotaxis, and phagocytosis might be needed to understand its mechanism.[24-26]

In the present study, nine patients with 25 episodes of recurrent DKA were noted. Type 1 diabetes (100%), female gender (77%), young age (18~27 years old, 77%), and omission of insulin (52%) were the characteristics of patients with recurrent DKA. Similar to our findings, a longitudinal study of young adults with type 1 diabetes showed that women were more likely to have multiple medical complications and psychiatric disorders.[27] This suggests that young females with type 1 diabetes need better education, communication, attention, family and psychosocial support to prevent recurrent DKA and other serious acute and chronic complications.

Of the two most common types of hyperglycemic crises, DKA is considered to occur more often in patients type 1 diabetes, and the hyperglycemic hyperosmolar state most frequently arises in patients with type 2 diabetes. Our results showed that 22% (11/49 cases) of patients with newly diagnosed diabetes presenting with DKA did not seem to have typical type 1 diabetes because they were insulin independent for more than 1.5 years after DKA. However we did not check β-cell autoantibodies or HLA typing, and the 1.5-year follow-up period was relatively short. Similar observations have been described globally in African-American patients,[6-9] Mexican-American patients,[10] Japanese men,[11] and Taiwanese patients[12] by various researchers. The term "ketosis-prone diabetes" was proposed by Maldonado et al.,[13] who demonstrated heterogeneity of β-cell autoimmunity and β-cell reserves among patients with DKA. Further understanding of the mechanism of ketosis-prone diabetes might contribute to revision of the diabetes classification.[28]

In conclusion, the mortality rate of patients with DKA has decreased since 1981 at our hospital. This may be due to a decrease in life-threatening co-morbid diseases. Bacterial infection, especially *Klebsiella pneumoniae*, was an important factor contributing to DKA. Young females with type 1 diabetes are susceptible to the recurrence of DKA and further efforts to prevent DKA in this population are necessary.

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糖尿病酮酸中毒：比較現今以及20年前病人特性、臨床表現和治療結果之異同

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背 景： 比較本院現今以及20年前糖尿病酮酸中毒(diabetic ketoacidosis)病人的臨床表現和治療結果。

方 法： 本回顧性研究是針對2001年1月至2002年6月在林口長庚醫院治療的糖尿病酮酸中毒病人，分析其臨床表現，誘發因子，實驗室檢驗資料，治療結果，並比較現今以及20年前糖尿病酮酸中毒病人在這些項目的異同。

結 果： 在1年6個月的研究期間總共有132位病人發生148次糖尿病酮酸中毒。和20年前本院的糖尿病酮酸中毒病患相比較，兩組的病人在臨床表現、誘發因子以及實驗室檢驗資料是相似的，但是死亡率由20年前的7.96%降至目前的0.67%。由細菌培養證實細菌感染的病人中，克列伯氏肺炎菌是誘發糖尿病酮酸中毒的主要菌種 (70%)。患有第1型糖尿病的年輕女性(67%)是重覆發生糖尿病酮酸中毒的高危險族群，其誘發因素以停用胰島素最常見。在現今的研究發現，49位以糖尿病酮酸中毒發作才診斷的糖尿病人中，有11位病人在後續的1.5年以上的追蹤可以停用胰島素。

結 論： 本院目前的糖尿病酮酸中毒病患在臨床表現以及誘發因子和20年前是相似，但是死亡率已有明顯降低。克列伯氏肺炎菌是本院細菌感染誘發糖尿病酮酸中毒中最常見的菌種。年輕女性患有第1型糖尿病是重覆發生糖尿病酮酸中毒的高危險族群。

(長庚醫誌 2005;28:24-30)

關鍵字：第1型糖尿病，糖尿病酮酸中毒，克列伯氏肺炎菌。

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受文日期：民國 93 年 1 月 4 日；接受刊載：民國 93 年 11 月 15 日。
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