Clinical characteristics of hyperglycemic crises in patients without a history of diabetes

Willy Chou¹²†, Min-Hsien Chung⁴⁸⁹, Hsien-Yi Wang⁵⁶, Jiann-Hwa Chen⁷⁸, Wei-Lung Chen⁷⁸, How-Ran Guo⁹¹⁰, Hung-Jung Lin³¹¹₁₂, Shih-Bin Su¹³¹⁴¹⁵, Chien-Cheng Huang³¹⁶*, Chien-Chin Hsu³¹¹*  

Departments of ¹Emergency Medicine and ¹¹Medical Research, Chi-Mei Medical Center, Liouying, Departments of ²Physical Medicine and Rehabilitation, ³Emergency Medicine, ⁴Nephrology and ⁵Occupational Medicine, Chi-Mei Medical Center, ⁶Department of Sport Management, College of Leisure and Recreation Management, ⁷Department of Recreation and Health Care Management, Chia Nan University of Pharmacy and Science, ⁸Department of Environmental and Occupational Health, Medical College, ⁹Department of Occupational and Environmental Medicine, National Cheng Kung University; Departments of ¹⁰Biotechnology, ¹¹Leisure, Recreation and Tourism Management and ¹²Child Care and Education, Southern Taiwan University of Science and Technology, Tainan, ¹³Department of Emergency Medicine, Cathay General Hospital, ¹⁴Fu Jen Catholic University School of Medicine and ¹⁵Department of Emergency Medicine, Taipei Medical University, Taipei, Taiwan

Keywords  
Hyperglycemic crisis, Mortality, New-onset

Correspondence  
Chien-Cheng Huang  
Tel: +886-6-281-2811  
Fax: +886-6-281-6161  
E-mail address: chienchenghuang@yahoo.com.tw and Chien-Chin Hsu  
Tel: +886-6-281-2811  
Fax: +886-6-281-6161  
E-mail address: nych2525@gmail.com

J Diabetes Invest 2014; 5: 657–662  
doi: 10.1111/jdi.12209

INTRODUCTION  
Hyperglycemic crises present a disease continuum of diabetic emergency. The basic underlying mechanism is the combination of absolute or relative insulin deficiency, and an increase in the counterregulatory hormones glucagon, catecholamines, cortisol and growth hormone.⁷ There are three types of hyperglycemic crisis: (i) diabetic ketoacidosis (DKA); (b) hyperosmolar hyperglycemic state (HHS) ([i] and [ii] are two extremes of the same clinical syndrome); and (iii) mixed syndrome (both DKA and HHS as a mixed state of acidosis and hyperosmolarity).²⁻⁷

The incidence and the cost of treating hyperglycemic crises are increasing. The annual incidence of DKA has been estimated to be 4.6–8 episodes per 1,000 patients with diabetes, and recent epidemiological studies in the USA report that the incidence sharply increased during the past two decades.³ There were 136,510 hospitalizations for DKA reported in the USA in 2006.⁸ The average cost per patient per hospitalization was US $13,000, and the annual medical expenditure for healthcare providers to patients with DKA might exceed US$1 billion.⁹ The incidence and medical expenditure for HHS care are unknown, because there are only a few population-based studies on HHS, and because many patients with HHS have multiple comorbidities. The rate of hospital admission for HHS was estimated to be 1% of all primary diabetic admissions.⁹ The
mortality rate for hyperglycemic crises remains high: 1–9% for DKA, 5–45% for HHS and 5–25% for mixed DKA/HHS.1,4,5,10 Among the elderly (aged ≥65 years), the mortality rate for hyperglycemic crises was recently reported to be as high as 71%.11

Interestingly, one-third of the patients with hyperglycemic crises were not diagnosed with diabetes (i.e., new-onset diabetes or without history of diabetes). New-onset diabetes is the third predisposing factor for a hyperglycemic crisis.4,10 The majority (92%) of these newly diagnosed patients had type 2 diabetes and presented with DKA (29%), HHS (40%) or DKA/HHS (31%).4 However, the clinical characteristics and predictors for the outcomes in these cases are not clear in the literature. We carried out this study to: (i) delineate the clinical characteristics, including the glycated hemoglobin (HbA1c) level of hyperglycemic crisis in patients without a history of diabetes; and (ii) compare this group with the other group of patients with a hyperglycemic crisis and a history of diabetes.

MATERIALS AND METHODS
Study Design, Setting, Population and Selection of Participants
The present study was carried out in a 700-bed university-affiliated medical center in Taipei, Taiwan, with a 40-bed emergency department (ED) and approximately 55,000 patients per year. Consecutive adult patients (aged >18 years) visiting the ED between January 2004 and December 2010 were enrolled if they met the following criteria:12 (i) DKA defined as plasma glucose >250 mg/dL, a high anion gap metabolic acidosis (anion gap >10, serum HCO3 <18 mmol/L and pH <7.3) and positive urine ketones or serum ketones; (ii) HHS defined as plasma glucose >600 mg/dL, increased effective serum osmolality >320 mOsm/kg, anion gap <12, no significant acidosis (HCO3 >15 mmol/L or pH >7.3), small urine ketones or serum ketones and an alteration in mental state; (iii) mixed syndrome (DKA plus HHS) defined as acidosis (pH <7.3, HCO3 <18 mmol/L), positive urine ketones or serum ketones and effective serum osmolality >320 mOsm/kg. The effective serum osmolality was calculated with the formula: 2 (measured Na [mEq/L]) + [glucose (mg/dL)] / 1812. There might be overlaps among the three types of hyperglycemic crisis, but because we were dealing with all three types of hyperglycemic crises as a whole, the overlaps should not affect the present study results.

Data Collection
All treatment of hyperglycemic crises strictly followed the guidelines suggested by the American Diabetes Association (ADA).1,3,12 Patients were prospectively selected in the ED. Information that was lacking was retrospectively collected by checking medical records. The study hospital’s Human Investigation Committee approved the protocol. The reviewers were blinded to the patients’ hospital course and outcomes. Information for a number of variables of each patient was recorded (Table 1).

Definition of Variables
The criteria of type 1 and type 2 diabetes were defined according to the guidelines of the ADA.13 Patients who denied and had no medical record of diabetes were classified as the group without a history of diabetes. The diagnosis of infection was based on laboratory and image results (such as pneumonia on a chest radiograph, pyuria on urinary analysis, abscess on computed tomography, etc.). The source of infection included lower respiratory tract infection, urinary tract infection, intra-abdominal infection, skin or soft-tissue infection, meningitis, bone/joint infection, perianal abscess, psoas muscle abscess, infective endocarditis and sepsis without focus.

A total of 368 ED patient visits met the criteria of a hyperglycemic crisis; 38 patients were excluded because of insufficient data or treatment in other hospitals. A total of 330 patient visits were enrolled. The enrolled patients were divided into two groups: without a history of diabetes and with a history of diabetes. We analyzed variables between these two groups, and evaluated HbA1c in the patients without a history of diabetes. Figure 1 shows the study flowchart.

Definition of End-Point
We used 30-day mortality as the primary end-point. People who survived at least 30 days whether or not they were still hospitalized were considered ‘survivors’ for this analysis. We used 30-day mortality as the primary end-point because the hospital stay of 93.6% patients was within 30 days in the present study. In addition, 30 days is a universally acceptable end-point for outcome studies.

Data Analysis
All analyses were carried out using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous data are means ± standard deviation. Comparisons between two groups were made using either an independent-samples t-test (assuming normal distribution) or Mann–Whitney/Wilcoxon tests (assuming non-normality) of the continuous variables. Either a χ2-test or a Fisher’s exact test was used for categorical variables. Significance was set at P < 0.05 (two tailed) to extract variables effective in a model.

RESULTS
A total of 330 patient visits by 295 individual patients, approximately 0.09% of all ED visits, were analyzed in the study period. Patients without a history of diabetes presented with 24.5% of the hyperglycemic crises (Table 1). There were significant differences between patients without and with a history of diabetes: younger 54.3 ± 20.2 years vs 62.5 ± 21.3 (P = 0.003), elderly 30.9% vs 55.4% (P < 0.001), male predominant 63.0% vs 44.6% (P = 0.004), having higher Glasgow coma scale 13.6 ± 3.0 vs 12.5 ± 3.5 (P = 0.007), less altered mental status 25.9% vs 39.8 (P = 0.025), presenting with thirst 43.2% vs 10.4% (P < 0.001), polydipsia 34.6% vs 6.0% (P < 0.001), polyuria 39.5% vs 8.4% (P < 0.001), bodyweight loss 32.1% vs
Table 1: Comparison of the clinical characteristics of patients with a hyperglycemic crisis without and with a history of diabetes.

| Variable                          | History of diabetes | All (n = 330) | P-value |
|-----------------------------------|---------------------|---------------|---------|
|                                   | Without (n = 81)    | With (n = 249)|         |
| Age (years)                       | 54.3 ± 20.2         | 62.5 ± 21.3   | 60.5 ± 21.3 | 0.003 |
| Elderly, aged ≥65 years (%)       | 30.9                | 55.4          | 49.4     | < 0.001 |
| Sex, male (%)                     | 63.0                | 44.6          | 40.1     | 0.004 |
| Vital signs                       |                     |               |          |
| Glasgow coma scale                | 13.6 ± 3.0          | 12.5 ± 3.5    | 12.8 ± 3.4 | 0.007 |
| Altered mental status (%)         | 25.9                | 39.8          | 36.4     | 0.025 |
| SBP                               | 140.0 ± 25.1        | 134.9 ± 34.4  | 136.3 ± 32.4 | 0.13  |
| Heart rate                        | 1110 ± 220.0        | 111.5 ± 238   | 111.4 ± 23.3 | 0.846 |
| Body temperature                  | 368.8 ± 1.1         | 368.8 ± 1.2   | 368.8 ± 1.1 | 0.694 |
| Respiratory rate                  | 204.4 ± 3.9         | 209.7 ± 5.3   | 208.2 ± 5.0 | 0.398 |
| Symptoms/signs (%)                |                     |               |          |
| Thirst                            | 43.2                | 104           | 185      | < 0.001 |
| Polydipsia                        | 34.6                | 6.0           | 13.0     | < 0.001 |
| Polyuria                          | 39.5                | 8.4           | 16.1     | < 0.001 |
| Bodyweight loss                   | 32.1                | 5.1           | 11.5     | < 0.001 |
| Medical history (%)               |                     |               |          |
| Hypertension                      | 38.3                | 45.6          | 45.4     | 0.191 |
| Stroke                            | 11.1                | 20.9          | 18.5     | 0.05  |
| Chronic renal insufficiency       | 0                   | 16.9          | 12.7     | < 0.001 |
| Cancer                            | 8.6                 | 8.4           | 8.5      | 1.000 |
| Nasogastric tube feeding          | 3.7                 | 10.8          | 9.1      | 0.073 |
| Bedridden                         | 7.4                 | 15.3          | 13.3     | 0.09  |
| Nursing home resident             | 0                   | 3.6           | 2.7      | 0.12  |
| Laboratory data                   |                     |               |          |
| Blood glucose (mg/dL)             | 852.3 ± 378.0       | 700.7 ± 293.7 | 737.9 ± 322.5 | 0.001 |
| WBC (cells/mm³)                   | 134000 ± 5788.2     | 127000 ± 5903.2 | 129000 ± 5874.8 | 0.335 |
| Hemoglobin (g/dL)                 | 156.6 ± 26.6        | 13.3 ± 29     | 13.9 ± 3.0 | < 0.001 |
| Platelet (1,000/mm³)              | 240.3 ± 74.7        | 235.5 ± 95.7  | 236.7 ± 90.9 | 0.638 |
| Osmolality (mOsm/kg)*             | 323.8 ± 32.2        | 325.9 ± 30.2  | 325.4 ± 30.7 | 0.581 |
| Blood urea nitrogen (mg/dL)       | 34.1 ± 23.7         | 48.7 ± 33.2   | 45.1 ± 31.7 | < 0.001 |
| Serum creatinine (mg/dL)          | 1.8 ± 0.8           | 2.2 ± 1.6     | 2.1 ± 1.5 | 0.001 |
| Blood PH†                         | 7.3 ± 0.1           | 7.3 ± 0.1     | 7.3 ± 0.1 | 0.333 |
| HbA1c (%)                         | 11.9 ± 2.9          | 11.7 ± 3.1    | 11.7 ± 3.0 | 0.571 |
| Precipitating factor (%)‡         |                     |               |          |
| Poor compliance                   | NA                  | 80.9          | 60.3     | NA   |
| Infection                         | 28.4                | 50.6          | 45.2     | < 0.001 |
| Pancreatitis                      | 2.4                 | 3.3           | 3.0      | > 0.95 |
| Acute coronary syndrome           | 0                   | 3.7           | 2.7      | 0.119 |
| Stroke                            | 1.2                 | 1.6           | 1.5      | > 0.95 |
| Subgroup diagnosis (%)            |                     |               |          |
| DKA                               | 370                 | 29.7          | 31.5     | 0.218 |
| HHS                               | 469                 | 59.4          | 56.4     | 0.048 |
| Mixed DKA/HHS                     | 160                 | 108           | 12.1     | 0.212 |
| 30-day mortality rate (%)         | 3.7                 | 12.9          | 10.6     | 0.021 |

Data are means ± standard deviation unless otherwise indicated. *Effective serum osmolality: 2 (measured Na⁺ [mEq/L] + glucose [mg/dL]) / 18. 191.8% (303/330) of the patients had this test. †Patients might have multiple precipitating factors. DKA, diabetic ketoacidosis; HbA1c, glycated hemoglobin; HHS, hyperosmolar hyperglycemic state; NA, not applicable; SBP, systolic blood pressure; WBC, white blood cell count.

5.1% (P < 0.001), without chronic renal insufficiency 0% vs 16.9% (P < 0.001), with higher level of blood glucose 852.3 ± 378.0 mg/dL vs 700.7 ± 293.7 mg/dL (P = 0.001), higher hemoglobin 15.6 ± 2.6 g/dL vs 13.3 ± 2.9 g/dL (P < 0.001), but with lower blood urea nitrogen 34.1 ± 23.7 mg/dL vs 48.7 ± 33.2 mg/dL (P < 0.001), lower serum creatinine 1.8 ± 0.8 mg/dL vs 2.2 ± 1.6 mg/dL (P = 0.001), less clinical presentation of infection 28.4% vs
50.6% ($P < 0.001$), fewer cases of 30-day mortality 3.7% vs 12.9% ($P = 0.021$) and less in the subgroup of HHS 46.9% vs 59.4% ($P = 0.048$). In the patients without a history of diabetes, all three patients who died within 30 days succumbed to sepsis. In the patients with a history of diabetes, 27 of the 32 patients (84.4%) who died succumbed to sepsis, one patient (3.1%) to sepsis with an acute coronary syndrome, one patient to sepsis with end-stage cancer, two patients to hypokalemia and one patient to an acute coronary syndrome.

The analysis showed that 88.9% (72/81) of the patients without a history of diabetes had new-onset type 2 diabetes and 11.1% had type 1 diabetes; that 93.8% (76/81) had HbA1c $\geq 6.5$%; and that just 6.2% (5/81) had HbA1c < 6.5% (Table 2). All the five cases described in Table 2 were proved to be type 2 diabetes after investigation. We also summarized the clinical characteristics of three mortality cases with hyperglycemic crisis without history of diabetes in Table 3.

**DISCUSSION**

The present study delineated the clinical characteristics of patients without a hyperglycemic crisis and with a history of diabetes. We found that patients without a history of diabetes were younger, predominately male, and had better consciousness and renal function, more significant diabetic signs and symptoms (thirst, polydipsia, polyuria and bodyweight loss), higher blood sugar, and a lower incidence of infection and infection.

**Table 2 | Clinical characteristics of five patients with hyperglycemic crisis with glycated hemoglobin < 6.5% and without a history of diabetes**

| Patient# | Age (years) | Sex | Medical history | HbA1c (%) | GCS | Glucose (mg/dL) | Osmolality (mOsm/kg) | Subgroup diagnosis | Outcome |
|----------|-------------|-----|-----------------|-----------|-----|-----------------|---------------------|-------------------|---------|
| 1        | 40          | Male| Nil             | 5.7       | 15  | 681             | 321.5               | Mixed             | Survival |
| 2        | 55          | Male| CAD             | 6.4       | 15  | 1019            | 329.5               | HHS              | Survival |
| 3        | 35          | Female| Nil          | 6.2       | 15  | 673             | 323.5               | Mixed             | Survival |
| 4        | 86          | Female| HTN Dementia   | 6.1       | 14  | 1230            | 382.9               | HHS              | Survival |
| 5        | 52          | Male| Nil             | 6.0       | 14  | 539             | 286.7               | DKA              | Survival |

CAD, coronary artery disease; DKA, diabetic ketoacidosis; GCS, Glasgow coma scale; HbA1c, glycated hemoglobin; HHS, hyperosmolar hyperglycemic state; HTN, hypertension.
mortality. We believe the difference is mainly due to the fact that patients without a history of diabetes (i.e., new-onset diabetes) were younger (and thus had better consciousness and renal function, more significant diabetic signs and symptoms, and lower mortality) and had a shorter duration of being diabetic (and thus had better renal function, more significant diabetic signs and symptoms, and lower mortality). The main reason why they had higher plasma glucose is probably due to the fact they were not treated for diabetes. It is less clear why there was a male predominance, but we suspect that might be attributable to more opportunities to eat a lot of food at one time, such as at social occasions. Most patients without a history of diabetes (93.8%, 76/81) had HbA1c ≥6.5%, which raised the argument of routine screening of diabetes using this biomarker.

Notably, 25% of the patients who presented with a hyperglycemic crisis were newly diagnosed with diabetes at the time of admission. This finding is similar to that in a population survey in Jamaica that reported that 32% of individuals were unaware of their hyperglycemic state. These patients are thus at high risk for presentation with a hyperglycemic crisis, because they are ignorant of the early warning signs of these crises. The high prevalence of diabetes combined with the risk that a hyperglycemic crisis could be the first clinical presentation gives credence to the usefulness of the concept of screening for diabetes for early detection. However, screening for diabetes is not universally accepted.

HbA1c, which is formed by the attachment of glucose to various amino groups of hemoglobin, and has been used since 1977 for the long-term (2–3 months) glycemic control follow up of diabetes, has recently been advocated by the ADA as a diagnostic tool. In 2009, the International Expert Committee of the ADA issued a statement proposing a HbA1c value of 6.5% (48 mmol/mol) as a diagnostic level for a diagnosis of diabetes. In 2010, the Committee of the Japan Diabetes Society also adopted HbA1c as a part of diagnostic criteria. This value was chosen because it was the value after which the incidence of retinopathy, a common complication often present before the actual diagnosis of diabetes is made, increases. In the present study, HbA1c ≥6.5% had a sensitivity of 93.8% (95% confidence interval 85.6–97.7%) for diagnosing diabetes in patients without a history of diabetes. If the diagnostic level of HbA1c was set to ≥6.0%, the sensitivity would be raised to 98.8% (95% confidence interval 92.4–99.9%).

Nevertheless, the present study had several limitations. First, some data were collected from a retrospective chart review. These clinical presentations or records might not have been completely documented. Second, this was a single-center study. Findings from our database might not be generalizable in other settings. Third, we did not investigate the origins of cancers that associate with 30-day mortality of patients with hyperglycemic crises and without a history of diabetes. Fourth, we did not investigate the presence or absence of soft drink intake, which often causes hyperglycemic crises in younger generations. Fifth, the whole sample size might not be large enough to draw conclusions with good statistical power. Additional studies with larger sample sizes are necessary.

ACKNOWLEDGMENTS

This study was supported in part by Grant CMFHR 10211 and CMNCKU10216 from the Chi-Mei Medical Center. We thank Bill Franke for his invaluable advice and editorial assistance. No potential conflicts of interest relevant to this article were reported.

REFERENCES

1. Kitabchi AE, Umpierrez GE, Miles JM, et al. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009; 32: 1335–1343.
2. Wachtel TJ, Tetu-Mouradjian LM, Goldiabetesan DL, et al. Hyperosmolarity and acidosis in diabetes mellitus: a three-year experience in Rhode Island. J Gen Intern Med 1991; 6: 495–502.
3. Kitabchi AE, Umpierrez GE, Murphy MB, et al. Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association. Diabetes Care 2006; 29: 2739–2748.
4. Chung ST, Perue GG, Johnson A, et al. Predictors of hyperglycaemic crises and their associated mortality in Jamaica. Diabetes Res Clin Pract 2006; 73: 184–190.
5. Mclsaac RJ, Lee LY, McNeil KJ, et al. Influence of age on the presentation and outcome of acidic and...
hyperosmolar diabetic emergencies. *Intern Med J* 2002; 32: 379–385.

6. Magee MF, Bhatt BA. Management of decompensated diabetes. Diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome. *Crit Care Clin* 2001; 17: 75–106.

7. Carroll P, Matz R. Uncontrolled diabetes mellitus in adults: experience in treating diabetic ketoacidosis and hyperosmolar nonketotic coma with low-dose insulin and a uniform treatment regimen. *Diabetes Care* 1983; 6: 579–585.

8. National Center for Health Statistics (2012) National Hospital Discharge Survey. Available from http://www.cdc.gov/nchs/nhds.htm, accessed 25 November 2013.

9. Fishbein HA, Palumbo PJ. Acute metabolic complications in diabetes. In: National Diabetes Data Group. Diabetes in America. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 1995; 283–292.

10. Huang CC, Kuo SC, Chien TW, et al. Predicting the Hyperglycemic Crisis Death (PHD) score: a new decision rule for emergency and critical care. *Am J Emerg Med* 2013; 31: 830–834.

11. Wang J, Williams DE, Narayan KM, et al. Declining death rates from hyperglycemic crisis among adults with diabetes, U.S., 1985–2002. *Diabetes Care* 2006; 29: 2018–2022.

12. Kitabchi AE, Umpierrez GE, Murphy MB, et al. Management of hyperglycemic crises in patients with diabetes. *Diabetes Care* 2001; 24: 131–153.

13. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2010; 33(Suppl 1): S62–S69.

14. The International Expert Committee. International Expert Committee report on the role of the A1c assay in the diagnosis of diabetes. *Diabetes Care* 2009; 32: 1327–1334.

15. Seino Y, Nanjo K, Tajima N, et al., Committee of the Japan Diabetes Society on the diagnostic criteria of diabetes mellitus. Report of the Committee on the Classification and Diagnostic Criteria of Diabetes Mellitus. *J Diabetes Invest* 2010; 1: 212–228.