JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

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

Willy Chou[1,2]†, Min-Hsien Chung[3,4]†, Hsien-Yi Wang[5,6], Jiann-Hwa Chen[7,8], Wei-Lung Chen[7,8], How-Ran Guo[9,10], Hung-Jung Lin[3,11,12], Shih-Bin Su[13,14,15], Chien-Cheng Huang[3,16]*, Chien-Chin Hsu[3,11]*

Departments of [4]Emergency Medicine and [15]Medical Research, Chi-Mei Medical Center, Liouying, Departments of [1]Physical Medicine and Rehabilitation, [3]Emergency Medicine, [5]Nephrology and [13]Occupational Medicine, Chi-Mei Medical Center, [6]Department of Sport Management, College of Leisure and Recreation Management, [2]Department of Recreation and Health Care Management, Chia Nan University of Pharmacy and Science, [9]Department of Environmental and Occupational Health, Medical College, [10]Department of Occupational and Environmental Medicine, National Cheng Kung University, Departments of [11]Biotechnology, [14]Leisure, Recreation and Tourism Management and [16]Child Care and Education, Southern Taiwan University of Science and Technology, Tainan, [7]Department of Emergency Medicine, Cathay General Hospital, [8]Fu Jen Catholic University School of Medicine and [12]Department 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

ABSTRACT

Aims/Introduction: Hyperglycemic crises without a history of diabetes have not been well studied. We compared the clinical characteristics of patients with and without a history of diabetes, and evaluated the glycated hemoglobin levels.

Materials and Methods: Consecutive adult patients (aged >18 years) visiting the emergency department (ED) between January 2004 and December 2010 were enrolled if they met the criteria for a hyperglycemic crisis. Patients were separated into those without and those with a history of diabetes. The 30-day mortality was the primary end-point.

Results: We enrolled 295 patients who made 330 visits to the ED. Patients without a history of diabetes made up 24.5% (81/330) of the hyperglycemic crises. Patients without a history of diabetes were more prone than patients with a history of diabetes to be younger and male, and to have better consciousness and renal function, more significant diabetic signs and symptoms (e.g., thirst, polydipsia, polyuria and bodyweight loss), higher blood sugar, and less opportunity of infection and mortality. Most of the patients (93.8%, 76/81) had glycated hemoglobin of ≥6.5%.

Conclusions: The present study delineates the clinical characteristics of patients with hyperglycemic crises, but without a history of diabetes. Most patients had glycated hemoglobin ≥6.5%, which raises the argument of using this biomarker for routine screening of diabetes.

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[1]. 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 hyperosmolality)[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[3]. 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

†These authors contributed equally to this work as first authors.
Received 7 November 2013; revised 16 January 2014; accepted 20 January 2014

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)[1,4,10]. 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 HCO_3 <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 (HCO_3 >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, HCO_3 <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)] / 18[12]. 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 χ^2-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% (81/330) 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	111.0 ± 22.0	111.5 ± 23.8	111.4 ± 23.3	0.846
Body temperature	36.8 ± 1.1	36.8 ± 1.2	36.8 ± 1.1	0.694
Respiratory rate	20.4 ± 3.9	20.9 ± 5.3	20.8 ± 5.0	0.398
Symptoms/signs (%)				
Thirst	43.2	10.4	18.5	< 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/mm^3)	13400.0 ± 5788.2	12700.0 ± 5903.2	12900.0 ± 5874.8	0.335
Hemoglobin (g/dL)	15.6 ± 2.6	13.3 ± 2.9	13.9 ± 3.0	< 0.001
Platelet (1,000/mm^3)	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	37.0	29.7	31.5	0.218
HHS	46.9	59.4	56.4	0.048
Mixed DKA/HHS	16.0	10.8	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. †91.8% (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 glucose852.3 ± 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

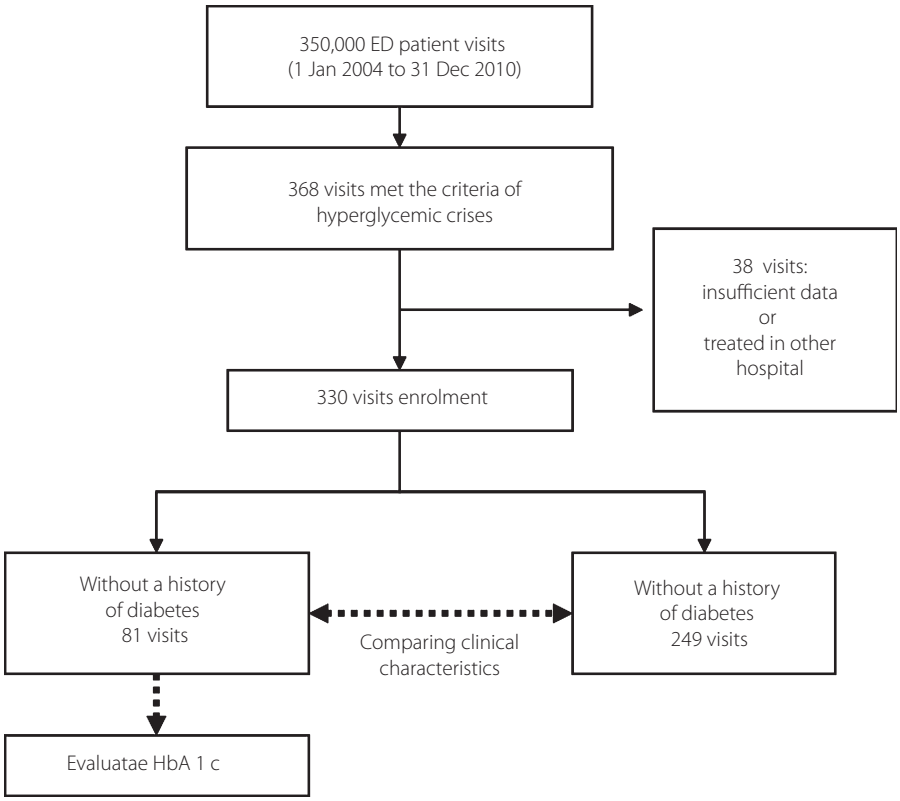

Figure 1 | Patient and visit enrolment, and separation to the two groups of without history of diabetes and with history of diabetes, and a flowchart of how the comparison and analysis of glycated hemoglobin (HbA1c) were carried out. ED, emergency department.

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 ≥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

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.

Table 3 | Clinical characteristics of three mortality cases with hyperglycemic crisis without history of diabetes

Age (years)	Sex	GCS	S/S	Medical history	Blood glucose (mg/dL)	Osmolality (mOsm/kg)	HbA1c (%)	Other precipitating factor	Subgroup diagnosis
72	Male	11	AMS	Cancer	321	285	10.5	Infection	DKA
85	Male	13	AMS Fever	Cancer HTN	609	321	10.9	Infection	HHS
87	Male	3	AMS Fever	HTN	610	337	11.5	Infection	HHS

AMS, altered mental status; DKA, diabetic ketoacidosis; GCS, Glasgow coma scale; HbA1c, glycated hemoglobin; HHS, hyperosmolar hyperglycemic state; HTN, hypertension; S/S, symptoms/signs.

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[4]. 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. However, screening for diabetes is not universally accepted[4].

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[14] 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[15]. 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[14]. 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. MacIsaac RJ, Lee LY, McNeil KJ, *et al.* Influence of age on the presentation and outcome of acidotic 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.