Clinical Profile of Adult Patients with Hyperglycemic Crisis at the De La Salle University Medical Center, A Ten-Year Retrospective Study

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Abstract

This current study aims to report the clinical profiles and characteristics of diabetic patients who had been admitted for hyperglycemic crises from 2007 to 2017 at our institution.

Methodology. We conducted a retrospective study in a tertiary care university hospital outside Metro Manila. The data gathered were divided into three categories: clinical data, biochemical data and precipitating factors.

Results. A total of 3,120 adult patients with diabetes mellitus were admitted for various reasons, and 71 cases presented with DKA or HHS over the 10-year period of review which is equivalent to 2% of all diabetes mellitus cases admitted. Forty-six (64.79%) of the patients with hyperglycemic crises were known diabetics with a duration of 7-13 years. Majority of patients were not taking anti diabetic medications upon admission. Most patients with hyperglycemic crises were tachycardic and hypertensive upon admission. Majority were discharged and improved. Majority of the cases 53 (81.69%) had DKA. The most common precipitating factor in DKA and HHS was infection.

Conclusion. In conclusion, the biochemical profiles in our series did not significantly differ from the past study by Gatbonton et.al (1998). Despite the advent of new therapies for diabetes mellitus control, mortality among the patients with hyperglycemic crises was slightly higher in our study at 11% compared to the global reported data of 2-10%. One of the reasons could be the minimal improvements in our health care delivery system that is still unable to cater to the needs of diabetic Filipinos. Early screening programs should be done for patients beginning age 40 years and even earlier for those with risk factors for prompt detection and treatment of diabetes mellitus. Education and awareness should be strengthened for patients with diabetes mellitus to avoid the crises by emphasizing the importance of regular follow-up, monitoring and compliance with a diabetic regimen, especially with insulin and multiple OADs (oral anti-diabetic drugs) since the disease is progressive, and timely intensification of therapy is needed.

Keywords: Type 2 diabetes mellitus, hyperglycemic crisis, oral-anti-diabetes drugs

Introduction

The first data on hyperglycemic crises was published 20 years ago, followed by a more recent review in 2020 from the same government institution. ^{21,36} We are reporting our data from a tertiary care hospital outside of the NCR catering to both private (70%) and charity (30%) patients. Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are the two most severe acute diabetic complications that have substantial morbidity and mortality if not adequately

treated in the promptly. It has a global mortality rate of 2-10%.¹ Diabetic ketoacidosis is generally linked to type 1 diabetes mellitus, but it also occurs in type 2 diabetes mellitus under conditions of extreme stress such as serious infection, trauma, cardiovascular or other emergencies. Less often, DKA may be the initial presenting manifestation in cases of ketosis-prone diabetes mellitus.² The two most commonly identified precipitating factors in the development of DKA were inadequate or incorrect insulin therapy and infection. Other precipitating factors included pancreatitis, myocardial infarction, cerebrovascular accident, and drugs 5

In the US, after a minimal decrease in hospitalizations for DKA last 2000-2009, there was a notable increase from 2009 to 2014 among all age groups, with the increase being highest among persons aged <45 years. Inpatient case-fatality rates among persons with DKA consistently decreased from 2000 to 2014.¹³ In the

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US and Canada, the incidence of DKA is approximately 20 cases per 1000 PYs (patient years) with a general reduction over the duration of study follow-up. ^{16,17} The most common precipitating factor is insulin omission in Canada. In the United Kingdom, DKA incidence rates ranged from approximately 8 cases per 1000 PYs.

HHS is estimated to be < 1% of hospital admissions of patients with diabetes mellitus, death occurs in 5-16% of patients with HHS, a rate that is approximately 10fold higher than that reported for DKA.³⁴ In a 5- year longitudinal study by Ivan Kruljac (2018), 68 HHS patients were older (74-86 years old) and infection was identified as one of the precipitating factors of HHS.²⁴ In Sweden, there was a numerical reduction in DKA cases with increasing incidence among patients aged from 18 to 24 years and they had a prevalence of 39 cases per 1000 people.^{19, 20} In Japan, the incidence of DKA was 0.48/1000 PYs and they identified the underuse of glucose-lowering medication as the common predisposing factor for DKA.²³ In a single institutional study in Korea, 78 patients fulfilled the criteria for DKA. Their mean age was 41.89 years. Sixtysix cases had prior history of diabetes mellitus, but DKA was the initial presentation in 12 cases. Among the cases, 24.4% were not on any treatment, 14.1% were using oral anti-diabetic drugs and 53.8% were on insulin. Poor glycemic control was the most common precipitating factor (56.4%).35 In Taiwan (2009), the incidence of DKA was 6/1000 to 5/1000 personyears.¹² In Thailand (2012), the incidence of hyperglycemic crises was 7.46%. DKA occurred more frequently than HHS (4.67% vs 1.71%). Infection was the most common precipitating factor (73.5%) followed by non-compliance with treatment (42.2%).²⁵

In the Philippines, data from 20 years ago described 61 episodes of hyperglycemic events Another local study by Gorgonia Padilla-Panilagao, 21 patients had hyperosmolar hyperglycemic nonketotic coma during a six-year period where in advanced age, stroke, glucocorticoid intake, and mannitol administration were the commonly identified risk factors.²² In the most recent retrospective review by Paragas et.al. in the Philippine General Hospital, 70 cases of DKA or HHS were gathered over a five-year period. The precipitating factors were also infection, withdrawal or non-adherence to insulin regimen and gastrointestinal disease, while 7% did not have any identifiable precipitating factor.³⁶

The developed countries had lower incidence of hyperglycemic crises as compared to the developing countries, understandably because of the better health care delivery system and access to medical services and medications. In the recent years, new diagnostic and monitoring tools such as HbA1c and point-of-care beta-hydroxy butyrate ketone level detection kits; and more therapeutic options such as insulin analogues, dipeptidyl-peptidase-4 inhibitor, **GLP-receptor** agonists and sodium-glucose-ligand transporter 2inhibitor could influence the incidence, presentation and management of hyperglycemic crises. Of note, the presentation of euglycemic DKA has documented with the use of sodium glucose cotransporter 2 inhibitors in diabetes mellitus in

pregnancy. 14,15 It would be interesting to note if any improvement in our local health care delivery system and access would affect the precipitating factors that cause hyperglycemic crises compared to 20 years ago.

Research Question. What was the clinical profile of adult patients with DKA and HHS in De La Salle University Medical Center from 2007 to 2017?

Objectives

General Objective: To determine the clinical and biochemical profile of adult patients with DKA and HHS at DLSUMC from 2007 to 2017.

Specific Objectives:

- 1. To describe the clinical profile of patients according to the following:
 - a. Demographic data
 - b. Type and duration of diabetes mellitus
 - c. Presenting signs and symptoms
 - d. Pre-admission anti diabetes mellitus medications
- 2. To describe the biochemical profile of patients according to the following:
 - a. Serum osmolality
 - b. Serum electrolytes
 - c. Arterial blood gas
- 3. To determine the precipitating factors for the development of DKA and HHS.

Study Setting and Design. This is a retrospective descriptive study that utilized data recorded in medical records of DLSUMC from 2007 to 2017.

Methodology

Population. The charts of all adult patients (>18yo) hospitalized at DLSUMC from 2007 to 2017 with an admitting diagnosis of DKA or HHS based on ICD-10 codes were reviewed. Patients fulfilling all the criteria for DKA and HHS according to Harrison's Principles of Internal Medicine 19th edition, were included (DKA: serum glucose of >250 mg/dL, serum bicarbonate concentration of <15mmol/L, arterial pH of <7.30, and with ketonemia [3mmol/L] and/or overt/significant ketonuria [>2+ on standard urine sticks]; HHS: serum glucose of 600 mg/dL, arterial pH of >7.3 and serum bicarbonate concentration of >20mmol, with absence or minimal ketonemia, and serum osmolality of >320mOsm/kg). Patients who were pregnant were excluded.

Operational definition of variables

- Serum Osmolality - a measure of the number of dissolved particles per unit of water in serum, calculated as: [[2xmeasured Na (mEq/l)] + [glucose (mg/dl)]/18].¹
- Length of stay the number of hospital days from admission to discharge.
- Level of consciousness classified as awake, lethargic, obtunded, and comatose
- Outcome categorized to the following: discharged improved, home against medical advice and expired.

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Precipitating Factors triggers hyperglycemic crises were categorized according to the following: Infection, noncompliance to medications, first presentation of DKA (no previous DKA episode), acute myocardial infarction, cerebrovascular disease.

Data Collection. The data gathered were divided into three categories: clinical data, biochemical data and precipitating factors. Clinical data included age, sex, duration and type of diabetes mellitus, smoking history, alcoholic beverage drinking history, vital signs, level of consciousness on admission, presenting signs and symptoms, co-morbidities, pre-admission antidiabetes mellitus medications, outcome hospitalization and length of stay in the hospital. Biochemical data included complete blood count (CBC), blood urea nitrogen (BUN), capillary blood glucose on admission, creatinine, sodium, potassium,

Table I. Clinical profile of participants according to type of hyperglycemic crisis.

Characteristics	DKA	HHS
	(n = 53)	(n = 18)
Age, years	50.96 ± 14.78	61.72 ± 4.46
Age distribution (years)		
19-30	4 (7.55%)	0
31-40	6 (11.32%)	1 (5.56%)
41-50	16 (30.19%)	5 (27.78%)
51-60	14 (26.42%)	3 (16.67%)
>60	13 (24.52%)	9 (50%)
Males	26 (49.06%)	8 (44.44%)
Duration of diabetes mellitus, years	6.33 ± 6.97	6.38 ± 4.46
Level of consciousness on admission		
Awake	47 (88.68%)	10 (55.56%)
Drowsy	4 (7.55%)	6 (33.33%)
Stuporous	1 (1.89%)	1 (5.56%)
Coma	1 (1.89%)	1 (5.56%)
Anti-diabetes mellitus medications		
OADS only	6 (11.32%)	7 (38.89%)
OADS with Insulin	18(33.96%)	5 (27.78%)
Insulin Only	1(1.89%)	0
No treatment	29 (54.72%)	6 (33.33%)
Non-smoker	42 (79.25%)	12 (66.67%)
Current Smoker	6 (11.32%)	4 (22.22%)
Previous Smoker	5 (9.43%)	2 (11.11%)
Non-alcoholic beverage drinker	38 (77.36%)	9 (44.44%)
Previous alcoholic beverage drinker	12 (22.64%)	1 (5.56%)
Current alcoholic beverage drinker	3 (5.67%)	8 (44.44%)
Co-morbidities		
Hypertension	7(13.20%)	12(66.67%)
Coronary Artery Disease	4(7.55%)	2(11.11%)
Chronic renal failure	3(5.56%)	2(11.11%)
Previous Stroke/Present Stroke	1(1.89%)/2(3.77%)	3(16.67%)
Heart Failure	0	2(11.11%)
Vital Signs on admission		
Heart rate, bpm	101 ± 22	100 ± 23
SBP, mmHg	126 ± 29	130 ± 28
DBP, mmHg	77 ± 14	79 ± 12
Respiratory rate	26±8	20±2
Temperature	36±2	37±2
Outcome of hospitalization		
Improved	46 (86.79%)	11 (61.11%)
Home against advice	2 (3.77%)	2 (11.11%)
Transferred to another hospital	1 (1.89%)	0
Expired	6 (11.32%)	5 (27.78%)
Length of Stay, days	4.53 ± 3.73	11.44 ± 2.98

chloride, arterial blood gas (pH and bicarbonate), HbA1c, serum osmolality and anion gap. Compliance or adherence to diabetic medications was based on the clinical history as documented in the hospital charts.

Data Analysis. Demographic data were recorded using descriptive statistics. Quantitative variables were reported as mean with standard deviation, while qualitative variables were reported as frequency and percentage.

Ethical Review. The study was submitted to the De La Salle - Health Sciences Institute Research Ethics Board Panel for ethics review and approval. Study was conducted only upon approval of the Panel. All patient information was anonymized and kept confidential. There were no conflicts of interest for the conduct of this study.

Subject Recruitment. Only records of patients were

utilized in this study. All patient names were recorded as patient codes to protect the identity of the patient. There was no direct participation of actual subjects as such there were no expected risks and direct benefits for the patient. No informed consent form was used. The principal investigator shouldered all the expenses in the study.

Results

A total of 3,120 patients were admitted with the diagnosis of diabetes mellitus over the 10-year period of review, of which 71 patients had DKA or HHS. Majority of the cases with hyperglycemic crises had type 2 DM, and only one DKA patient had T1DM. Our study showed that 25 patients (35.21%) had no known of diabetes mellitus presentation. Forty-six patients (64.79%) were known diabetics for a mean duration of 6 years. Most patients were awake at the time of admission. Almost half of our patients were on OADS (Oral Anti-Diabetic medications) alone, and one fifth were on insulin therapy. No one was on SGLT-2 inhibitor, alphaglucosidase inhibitor, meglitinides, nor GLP-Receptor Agonist. Few were and alcoholic beverage smokers drinkers. Only 6 patients had coronary artery disease, and no one had percutaneous coronary intervention. Only 2 HHS patients had heart failure. Hypertension was more common among patients with HHS 12(66.67%) than DKA 7(13.20%). Only 4 had previous history of stroke and only 2 had presented with stroke on admission. Only 3 DKA (5.66%) patients had chronic kidney disease (CKD) mostly at stage 2. Infection was identified as the main factor causing 37(69.81%) DKA and 8 (44.44%) HHS. Only 2 patients were on chronic steroid

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Table II.Percentage Distribution of presenting signs and symptoms according to type of Hyperglycemic crises

Signs and symptoms	DKA (n = 53)	HHS (n = 18)
Tachycardia	21 (39.62%)	8 (44.44%)
Hypotension	6 (11.32%)	1 (5.56%)
Tachypnea	15 (28.30%)	5 (27.78%)
Hypothermia	2 (3.77%)	0
Fever	13 (24.53%)	0
Confusion	1 (1.89%)	8 (44.44%)
Polyuria	13 (24.53%)	0
Abdominal Pain	19 (35.84%)	3 (16.67%)

Table III. Percentage distribution of pre-admission antidiabetes mellitus medications according to type of hyperglycemic crises

Anti-diabetes mellitus Medications	DKA (n = 53)	HHS (n = 18)
Oral anti-diabetic drugs		
Sulfonylureas	9 (16.09%)	12 (22.22%)
Gliclazide	6 (11.32%)	10 (55.56%)
Glibenclamide	3 (5.67%)	2 (11.11%) [´]
Thiazolinediones	6 (11.32%)	1 (5.56%)
Metformin	4 (7.55%)	0
DDP-4 inhibitor	1(1.98%)	0
Insulin Glulisine	1(1.89%)	0
Insulin Glargine	1(1.89%)	0
Human insulin premixed 70/30	9(16.98%)	12(22.22%)

Table IV. Biochemical profiles of patients according to type of Hyperglycemic Crisis

Blood parameters	DKA	HHS
Serum osmolality, mosm/kg	303 ± 15.64	331 ± 23.64
Serum creatinine, mmol/L	127 ± 77.24	188 ± 128.22
Serum Sodium, mM	132 ± 7.35	138 ± 7.24 mmol/L
Serum Chloride, mM	98 ± 7.93	98 ± 11.22 mmol/L
рН	7.24 ± 0.01	7.38 ± 0.12
Bicarbonate mEq/L	12 ± 6.83	19 ± 4.19
Hba1c	12.35±2.54 %	12.84±3.56 %
CBG upon admission	460±133 mg/dL	560±133mg/dL
Anion gap	22±6	29±10

Table V. Percentage distribution of identified precipitating factors according to type of hyperglycemic crises

Precipitating factors	DKA	HHS
Infection		
UTI	14 (26.42%)	9 (50%)
Pneumonia	9 (16.98%)	2 (11.11%)
Gastroenteritis	4 (7.55%)	0
Others (Fournier's gangrene)	1 (1.89%)	0
Non-compliance to medications	10 (18.87%)	6 (33.33%)
Others		
Acute myocardial infarction	3 (5.66%)	4 (22.22%)
Liver Cirrhosis	0	1 (1.89%)

Table VI. Causes of Mortality

Cause of Death	DKA	HHS
Septic Shock	4(66.67%)	1(20.00%)
Acute myocardial infarction	2(33.33%)	4(80.00%)

therapy for asthma. The mean Hba1c level among DKA patients is 12.35±2.54 % (range of 9 to 15 %) and 12.84±3.56 % (range of 9 to 17 %) among patients with HHS, although 12 charts did not have HBa1C but were included for analysis of other outcomes. The mean duration of hospital stay for patients with DKA was 4.53 ± 3.73 (range 1-9 days) and $11.44 \pm$ 2.98 (range 1-30 days) for patients with HHS. Most patients with hyperglycemic were tachycardic hypertensive upon admission. The capillary blood glucose range upon admission among DKA patients ranged from 327 to 593 mg/dL with a mean glucose level of 460 reading of 460±133 mg/dL; and ranged from 427 to 693mg/dL with a mean 560±133mg/dL for HHS patients. Majority were discharged improved 46 (86.79%) among patients with DKA; unfortunately, 6 (11.32%) expired. Consistent with established data, mortality was higher for HHS at 27.78% (Table I).

Clinical presentation was analyzed, and it was found out that tachycardia was present in a large number of patients 21 (39.62%) in DKA patients and 8(44.44%) in HHS patients. The most common presenting symptoms were abdominal pain 19 (35.84%) among DKA patients, and confusion among HHS patients 8 (44.44%) (Table II). Many patients with DKA were on premixed human insulin 9(16.98%). Among HHS patients, the most commonly prescribed diabetic medication before admission was premixed insulin metformin and 4(22.22%) (Table III). Most patients had elevated creatinine levels. The most common precipitating factor in DKA and HHS was infection (Tables IV and V).

Discussion

We presented the clinical profile, biochemical profile, and precipitating factors of DKA and HHS. It is noteworthy that out of over 3.000 admissions of patients with diabetes mellitus as part of the diagnosis, only 71 patients (2%) were actually admitted for hyperglycemic crises over a period of ten years. In our study there was female preponderance in patients with DKA which was similar to international studies. The age bracket with the highest incidence of DKA was 41 to 50 years old. In HHS patients, there gender no significant was preponderance, and it was usually seen patients. elderly Cases hyperglycemic crises due to poor compliance to medications which

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resulted in poor control of blood sugar levels seen in our setting, is identical to a report from other developing countries such as in Thailand which has a comparable health care system to ours. There was no mention of age range in the studies done internationally but hyperglycemic crises also occurred more frequently in older adults.^{22,3} Diabetes mellitus was present for a mean of duration of 6.33 ± 6.97 years (range 1 to 13) for DKA and an average of 6.38 ± 4.46 years (range 2 to 11) for HHS compared to the previous local study in DKA where the mean duration of diabetes mellitus presenting with hyperglycemic crises was 4 years. This may reflect slightly earlier intensification of the management of diabetes mellitus in current times, leading to improvement in overall longevity compared to 20 years ago.²¹ In the most current review in that same government hospital, 31% of the cases were newly-diagnosed DM but there was no mention of the duration of diabetes mellitus in the remaining cases with known DM.36

In our study, smoking was not prevalent in hyperglycemic crises as compared to international studies where DKA was correlated with smoking.³¹ Alcoholic beverage drinking was prevalent in patients with HHS similar to international and local studies.³² Hypertension was the most prevalent chronic underlying disease as part of the metabolic syndrome, and it was correlated with the patients' advancing age. Majority of acute underlying disease in patients with hyperglycemic crises was infection, which was seen in 69.81% of DKA patients and in 44.44% of the HHS patients. This is congruent with local and international studies, except with US data wherein it was only prevalent in patients with severe DKA.

The average length of stay among patients with DKA is 4.53±3.73 days and 11.44±20.98 days among patients with HHS. For the government hospital, the median length of stay in the ICU was 3 days followed by 7 days in the general ward with an overall range of 1 to 58 days.³⁶ In comparison, the previous local study in the same government hospital showed a length of stay of 13.36±13.97 days; this may reflect the improvement in the strategy for management of hyperglycemic crises hence shorter hospital stay in our study. The mean HbA1c in our study were 12.35±2.54% among DKA patients and 12.84±3.56% among HHS patients which were higher compared to an international study wherein the mean Hba1c was 10.86% which shows the worse control of diabetes mellitus among Filipinos.9 Admission HbA1c levels were not reported in the other local reviews published.^{21,22,36}

Majority of patients with DKA and HHS survived the crises, but the overall mortality rate was high at 15%; and based on specific type of crises it was 27.78% among HHS patients and 11.32% for those with DKA over the ten-year period reviewed. The most recent review reported at the government hospital the overall mortality was 23% over the five- year period which is higher than our study (15.49%). According to a study in India, the mortality rate in patients with DKA was less than 5% in experienced centers, 5%-15% in community hospitals and 30% of all intensive care cases.^{29,30} The mortality rate is largely based on the country's health

care capacity with DKA related mortality rates of 0.65% up to 3.3% in countries such as US, UK and Canada; whereas developing countries such as Kenya also reported a similar mortality rate of up to 30% like in India.^{29,30, 36-38} Hyperosmolar hyperglycemic state consistently has a much higher mortality rate of 20% even in developed countries.³⁹

The most common presenting symptom was abdominal pain which is comparable to other studies.3 All subjects in our data presented with hyperglycemic crises for the first time as compared with international studies where recurrent DKA admissions were included in the study. In the most recent data of the government hospital, they reported that 12.9% of their cases had previous history of hyperglycemic crises.³⁶ Majority of patients used biguanide, sulfonylureas and pre-mixed human insulin as pre-admission antidiabetes mellitus medication which were similar to international and local studies. Patients who hyperglycemic crises were mostly developed maintained on combination of OADS (oral antidiabetes medications); only 20-22% were on insulin- all of whom had poor control of diabetes mellitus prior to admission as reflected by the markedly elevated mean HBA1c exceeding 12%. This may reflect the delayed insulin initiation and inadequate titration seen in the overall clinical setting.

One of the most common precipitating factors in the patients with DKA in the study was infection particularly urinary tract infection followed by pneumonia, similar to the other two local studies; whereas with international studies, DKA was related to insulin therapy (e.g., missed insulin injection, change in insulin dose or regimen, problem with insulin pump). In HHS, infection, non-compliance with anti-diabetic medications and myocardial infarction were the most common precipitating factors similar to international studies.^{21,22}

The clinical characteristics of the study population had similarities and differences as compared to the other local studies. The similarities of the study were the following: the prevalence of DKA in DM type 2 was also higher than in DM type 1 reflective of the higher prevalence of type 2 DM compared to DM type 1 in the general population. The main precipitating factor for DKA was also infection and non-compliance with medications. The age range was also in the 40-50-year bracket and the biochemical profile was almost the same. The differences were the following: patients had mean diabetes mellitus duration of around six years compared to four years; abdominal pain was the predominant symptom rather than nausea and vomiting, and we were able to collect documentation of the HbA1c levels which were not reported in the other two publications. The duration of hospital stay and the mortality rate are also markedly lower at our institution compared to the government tertiary hospital which suggests the potential disparity in the provision of resources needed for more prompt diagnosis and overall management. similarities in terms of precipitating factors and poor pre-admission glycemic control among the three studies spanning over the past 20 years, these suggest

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that the health care delivery system had minimal change to address the availability and affordability of diabetic therapies. There is no health care coverage that could provide accessible testing, monitoring, and free medicines for diabetic patients. In terms of differences, there was the introduction of new therapies and diagnostics to help screen and monitor diabetes mellitus, and manage hyperglycemic crises better compared to 20 years ago. Our cases had longer duration of diabetes mellitus compared to the case series reported 20 years ago and this may reflect the overall increase in our longevity.

Conclusion

In conclusion, the study showed that in our country, hyperglycemic crises are usually present in previously undiagnosed cases of diabetes mellitus. At our tertiary care institution, 71 out of 3,120 cases with a diagnosis of diabetes mellitus (or 2%) were admitted for hyperglycemic crises over a period of ten years. Urinary tract infection, pneumonia, and non-compliance to diabetes mellitus regimen were common precipitants. Biochemical values did not significantly differ compared with the local study done 20 years ago. Mortality among hyperglycemic crises patients was just comparable to the data from countries with the same level of development; but better than the reported mortality rate in our government hospital. Health education should be strengthened for patients with diabetes mellitus to avoid the crises by stressing the importance of compliance to diabetic regimen especially with insulin. Timely intensification of treatment should be emphasized to both patients and medical practitioners in the management of diabetes mellitus. Prompt screening programs should be done for patients aged 40 years and above, and even earlier for those with risk factors for timely detection and treatment of diabetes mellitus among Filipinos.

Limitations. The main limitation of this study was that it was performed only in one institution. Twelve charts did not have HbA1c reading in this study. Predictors of mortality were not investigated.

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