The Incidence of In-Hospital Hypoglycemia and its Associated Risk Factors Among Adult Filipino Patients with Diabetes Mellitus in Chong Hua Hospital

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Abstract

Introduction: Hypoglycemia is a burdensome complication in the management of diabetes mellitus (DM), and has been noted to be increasing. This study evaluated the occurrence of hypoglycemia and identified its risk factors among diabetic Filipino patients.

Methods: Census of Filipino non-pregnant adults with type 2 DM of Chong Hua Hospital, admitted and discharged from January 2015 to June 2015 was taken. This study determined the incidence rate of hypoglycemia (capillary blood glucose <70 mg/dL), its severity, patients' dietary status, medication, and the common hospital areas where hypoglycemia occurred. The clinical profiles of these patients were analyzed and associated risk factors of hypoglycemia were identified. Also, the incidence of congestive heart failure, myocardial infarction, cerebrovascular disease, and all-cause mortality among patients with hypoglycemia were determined.

Results: Among 1,676 subjects, 8.9% had hypoglycemia predominantly non-severe type (blood glucose 51-69 mg/dL). The identified risk factors for the development of hypoglycemia were the following, age >65 years old (52.7% vs 36.2%, $p<0.001$), diabetes duration of 8.56 years (± 10.34 years), the presence of cardiovascular disease (62.7% vs 48.6%, $p<0.001$), congestive heart failure (8.7% vs 4.4%, $p=0.009$) and stage III, IV, V kidney disease (32.7% vs 25.1%, $p=0.043$, 12% vs 5.5%, $p=0.002$, 12% vs 4.1%, $p<0.001$, respectively), and the use of insulin whether combined with oral therapy (25.3% vs 16.5%, $p<0.006$) or used alone (34.7% vs 12.1%, $p<0.001$). Hypoglycemia occurred more frequently in the non-ICU ward (82.7%). Only one patient developed non-fatal myocardial infarction, one had non-fatal cerebrovascular disease and one had congestive heart failure. All-cause mortality rate was 4.7%

Conclusion: The notable incidence of in-hospital hypoglycemia of 8.9% among diabetic patients should be addressed to decrease the associated morbidity and mortality.

Keywords: hypoglycemia, diabetes, diabetes mellitus

Introduction

Hypoglycemia is a dangerous complication in the management of diabetes and precludes the achievement of glycemic control. Its incidence has been noted to be increasing and has added to the morbidity of the disease with resultant increased medical expenses. Hypoglycemia is defined as episodes of low plasma glucose concentrations, enough to cause symptoms or signs[1], and may expose the individual to potential harm. According to the American Diabetes Association (ADA), a blood serum glucose or capillary glucose <70 mg/dl is determined as hypoglycemia.[2]

It has been noted that the incidence of hypoglycemia is increasing. Among 1,718 adult patients admitted for hyperglycemia or receiving insulin therapy, this adverse event occurred on 2.8% of all hospital days.[3] In another study, hypoglycemia events were observed in 7.7% of admissions in a general ward.[4] Point-of-care bedside glucose monitoring in the hospitals in United States identified hypoglycemia prevalence of 6.3% of patient-days for intensive care unit (ICU) patients and 5.7% of patient-days for non-ICU patients.[5] In fact, National Diabetes Inpatient Audit reported in 2012 that in England, 22.4% of inpatients experienced at least one hypoglycemic episode.[6] An Asian study showed an incidence of 1.29% among hospitalized Chinese diabetic patients.[7]

Hypoglycemia can be classified as: mild, if with autonomic symptoms and the patient can treat himself; moderate, if with both autonomic and neuroglycopenic symptoms but still patient can manage by himself; and severe, if patient requires assistance from another person.[8] The episodes of severe hypoglycemia are a small fraction of the total hypoglycemia rate. The data from University Hospital Consortium showed that the prevalence of severe hypoglycemia ranged from three to 11%.[9] In unselected populations, the annual prevalence of severe hypoglycemia has been reported consistently at 30-40% in several

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large studies.[10] However, these reported incidences of hypoglycemia varies considerably among studies.

Both insulin-induced and spontaneous hypoglycemia increased the risk for mortality among hospitalized patients.[11] All three trials, Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation (ADVANCE), and Veterans Affairs Diabetes Trial (VADT), clearly demonstrated that an episode of severe hypoglycemia was associated with an increased risk of subsequent mortality. A retrospective analysis of 4,368 admissions involving 2,582 diabetic patients admitted to the general ward where indicated that severe hypoglycemia was associated with increased length of stay, greater odds of inpatient death, and death within one year of hospital discharge.[12] Deaths of up to 10% of patients with severe sulfonylurea-induced hypoglycemia have been reported. These are thought to be the result of cardiac arrhythmias triggered by an intense sympathoadrenal response resulting from QT interval prolongation and reduced baroreflex sensitivity.[1] Thus, early recognition and prompt management of hypoglycemia should be the proper practice to decrease the patient's morbidity and mortality.

Common risk factors for hypoglycemia include the following: mismatch of insulin timing and amount or type of carbohydrate intake; mismatch of oral secretagogues without appropriate carbohydrate intake; history of severe hypoglycemia; low glycosylated hemoglobin; presence of altered consciousness; reduction of oral intake; new nothing per orem (NPO) status; critical illness like hepatic, renal, and heart failure.[13]Identification of these risk factors during admission, with appropriate adjustments of diabetes mellitus (DM) treatment regimens, will reduce the patient's risk for in-hospital hypoglycemia.

To the best of our knowledge, there are no published studies about hypoglycemia in the Philippines. This study will determine the incidence of in-hospital hypoglycemia and identify its associated risk factors. The primary objective of this study was to determine the incidence and risk factors associated with hypoglycemia among the census of admitted diabetic patients in the local setting. The secondary objective of this study was to determine the incidence of all-cause mortality and morbidity (myocardial infarction, cerebrovascular disease and congestive heart failure) of patients who had hypoglycemic event.

Methods

Study design and population

This is a cross-sectional analytic study utilizing a retrospective review of charts of all the Filipino adults with type 2 DM of Chong Hua Hospital (CHH), admitted and discharged from January 2015 to June 2015.

Data collection and analysis

Patients with type 2 DM with recorded hypoglycemia were identified by their patient identification number. The chart retrieval and review was done through manual charts scanned and stored at the hospital medical records section. The clinical profile of these patients was collected and this included the gender, age, body mass index (BMI), duration of DM, available glycosylated hemoglobin (Diabetes Control and Complications Trial standardized) and creatinine values taken within one month of admission, and comorbidities such as cardiovascular disease and heart failure, liver cirrhosis, chronic kidney disease, and cancer. In the analysis of risk factors, patient records with incomplete data (eg. glycosylated hemoglobin or creatinine) were excluded

The information of only the first hypoglycemia occurrence was analyzed as to the severity of hypoglycemia, patient's diet status, diabetic pharmacologic therapy, hospital area of event, and the occurrence of congestive heart failure, myocardial infarction (fatal or nonfatal), cerebrovascular events (fatal or nonfatal), and all-cause mortality.

Hypoglycemia of <70 mg/dL was identified thru the point-of-care capillary blood glucose monitoring by trained nurses. The hospital-wide policy of only using the Lifescan's SureStepFlexx Meter (Johnson and Johnson Company), which was calibrated daily at 12 midnight, standardized the glucose monitoring of all inpatients. However, the frequency and the timing of its determination were limited to the medical decision of the attending physician.

Operational definition

1. Hypoglycemia – capillary blood sugar level of <70 mg/dL according to the ADA.[2]
   a. Non-severe hypoglycemia – capillary blood glucose level between 51-69 mg/dL, with or without symptoms
   b. Severe hypoglycemia – capillary blood glucose level 50 mg/dL and below, with or without symptoms
2. Body mass index (BMI) – calculated as weight in kilograms over height in meters squared. This is classified according to the Asian cut points as recommended by the ADA[14]:
   - Underweight – BMI <18 kg/m^2
   - Normal – BMI 18-22.9 kg/m^2
   - Overweight – BMI 23-24.9 kg/m^2
   - Obese – BMI ≥ 25 kg/m^2
3. Chronic kidney disease – estimated glomerular filtration rate (eGFR) is calculated thru the Chronic Kidney Disease Epidemiology (CKD-EPI) creatinine equation (2009)[15] and is classified as follows:
   Stage 1–normal eGFR of ≥ 90 ml/min/1.73 m^2

Stage 2 – mildly decreased eGFR of 60-89 ml/ min/1.73 m^2
Stage 3 – moderately decreased eGFR of 30-59 ml/ min/1.73 m^2
Stage4– severely decreased eGFR of 15-29 ml/min/1.73 m^2
Stage 5 – kidney failure with eGFR < 15 ml/min/1.73 m^2

4. Cardiovascular disease – patients with documented diagnosis of previous or present myocardial ischemia/ infarction, cerebrovascular diseases, peripheral arterial occlusive disease
5. Congestive heart failure – patients with documented diagnosis of congestive heart failure
6. Liver Cirrhosis – patients with documented diagnosis of liver cirrhosis
7. Cancer – patients with documented diagnosis of any type of cancer

Data management and statistical tools

Data from patients were encoded in Excel spreadsheets ver 2015. All patients' categorical profiles were described in frequency and percentage while those continuous or quantitative profiles were expressed in mean and standard deviation. Meanwhile, in comparing averages, Mann Whitney U non-parametric test was used while testing association, Chi-square test of independence with 2x2 Fisher's exact test was employed. Any associated *p*-values lesser than 0.05α were considered significant. IBMSPSS ver. 21 was used as statistical software.

Results

Incidence of Hypoglycemia

There was a total census of 1,676 patients with type 2 DM, admitted and discharged from January 1, 2015 to June 30, 2015, and had point-of-care blood glucose testing results. Only 150 patients experienced hypoglycemia and the incidence rate was 8.9% (Table I). Among the 150 cases of hypoglycemia, 88% (132/150) were categorized as non-severe (capillary blood glucose 51-69 mg/dL), while 12% (18/150) were severe (capillary blood glucose ≤ 50 mg/dL).

Clinical Profile

Patients who were >65 years old had higher frequency of hypoglycemia (52.7% vs 36.2%, $p<0.001$). There was an equal distribution of male and female patients and most of them had longer duration (8.56 years ± 10.34 years) of type 2 DM, as seen in Table II.

There was a greater proportion of patients belonging in the normal BMI category who experienced hypoglycemia. In contrast, those in the obese category, which was the majority of our patients, showed the lowest risk of having low blood sugar levels.

Table I. Incidence of in-hospital hypoglycemia among adult Filipino patients with DM

Hypoglycemia	No. of patients	Rate
With Hypoglycemia	150	8.9
Without hypoglycemia	1,526	91.1
Total DM	1,676	100

Hypoglycemia was noted more among younger patients (≤65 years old) who had higher glycosylated hemoglobin (HbA1c) values (61% vs 43%, $p=0.014$). For the older age group, those with HbA1c above eight showed more hypoglycemia episodes but was not statistically significant, while those with lower HbA1c levels experienced less hypoglycemia events during admission.

Comorbidities such as stage III (32.7% vs 25.1%, $p=0.043$), stage IV (12% vs 5.5%, $p=0.002$) and stage V (12% vs 4.1.%, $p<0.001$) kidney disease, cardiovascular disease (62.7% vs 48.6%, $p<0.001$), and congestive heart failure (8.7% vs 4.4%, $p=0.009$) put patients at higher risk for the development of hypoglycemia. The presence of liver cirrhosis (0.7%) and cancer (12%) were factors for the event.

As noted in Table III, the 150 cases had the following dietary status during the hypoglycemia event: 84% were on regular (oral) diet, 8% had nothing per orem, and 8% had tube feeding while in those 1,526 patients who did not experience hypoglycemia, 95.4% had oral diet, 2.6% had tube feeding, and two percent had nothing per orem.

Table IV shows that oral therapy alone did not show higher incidence of hypoglycemia. There was no difference between the use of sulfonylureas and other agents as monotherapy. However, there was a lower incidence of hypoglycemia among those with multiple oral therapy independent of sulfonylurea use (5.3% vs 16.2%, $p=0.001$). Use of insulin, whether combined with oral hypoglycemic agents (25.3% vs 16.5%, $p=0.006$), or alone (34.7% vs 12.1%, $p<0.001$) was significantly associated with the development of hypoglycemia. Among the combination therapy, the addition of sulfonylurea to an insulin regimen did contribute to the hypoglycemia occurrence (eight percent vs. four percent, $p=0.034$), while there is no significant difference as to which insulin dependent type hypoglycemia occurred more frequently. Premix human insulin, combined with non-sulfonylurea oral agents, also had higher hypoglycemia events (4.7% vs1.8%, $p=0.02$).

Basal-bolus regimen with a rapid-acting insulin (11.3% vs 3.9%, $p<0.001$), premix human insulin (7.3% vs2.1%, $p<0.001$), continuous insulin infusion with rapid-acting insulin (3.3% vs 0.1%, $p<0.001$) or short-acting insulin (1.3% vs 0.3%, $p=0.037$) and the giving of rapid-acting insulin as rescue dose (2% vs 0.2%, $p=0.001$) were the treatment modalities observed to

Table II. Clinical profile of patients

Characteristics	Without hypoglycemia n=1,526 (%)	With hypoglycemia n=150 (%)	Total n=1,676 (%)	*p*-value
Sex				
Females	767(50.3%)	75(50%)	842(50.2%)	0.951
Males	759(49.7%)	75(50%)	834(49.8%)	
Length of DM, average[SD]	5.28[7.47]	8.56[10.34]	5.56[7.83]	<0.001
BMI status				
Normal	331(21.7%)	44(29.3%)	375(22.4%)	0.032
Underweight	13(0.9%)	2(1.3%)	15(0.9%)	0.550
Overweight	272(17.8%)	33(22%)	305(18.2%)	0.206
Obese	910(59.6%)	71(47.3%)	981(58.5%)	0.004
Age				
Average[SD]	61.63[12.67]	66.47[11.61]	62.06[12.65]	<0.001
≤ 65 years old	974[63.8%]	71[47.3%]	1,045[62.4%]	<0.001
HbA1c	N=696	N=49	N=745	
<7.0	275[40%]	15[31%]	290[39%]	0.217
7.1-8.0	121[17%]	4[8%]	125[17%]	0.095
>8.1	300[43%]	30[61%]	330[44%]	0.014
> 65 years old	552[36.2%]	79[52.7%]	631[37.6%]	<0.001
HbA1c	N=342	N=50	N=392	
<8	263[77%]	31[62%]	294[75%]	0.023
8.1-9.0	33[10%]	8[16%]	41[10%]	0.171
>9.0	46[13%]	11[22%]	57[15%]	0.109
Kidney disease stage				
I	236(15.5%)	10(6.7%)	246(14.7%)	0.004
II	438(28.7%)	35(23.3%)	473(28.2%)	0.163
III	383(25.1%)	49(32.7%)	432(25.8%)	0.043
IV	84(5.5%)	18(12%)	102(6.1%)	0.002
V	63(4.1%)	18(12%)	81(4.8%)	<0.001
Cardiovascular disease	742(48.6%)	94(62.7%)	836(49.9%)	<0.001
Congestive Heart Failure	67(4.4%)	13(8.7%)	80(4.8%)	0.009
Liver cirrhosis	34(2.2%)	1(0.7%)	35(2.1%)	0.202
Cancer	189[12.4%]	18[12%]	207[12.4%]	0.891
Thyroid	19(1.2%)	3(2%)	22(1.3%)	
Breast	28(1.8%)	1(0.7%)	29(1.7%)	
Lung	17(1.1%)	4(2.7%)	21(1.3%)	
Esophageal	3(0.2%)	0(0%)	3(0.2%)	
Gastric	9(0.6%)	0(0%)	9(0.5%)	
Liver	30(2%)	2(1.3%)	32(1.9%)	
Cholangiocarcinoma	2(0.1%)	0(0%)	2(0.1%)	
Pancreatic	5(0.3%)	1(0.7%)	6(0.4%)	
Colon	35(2.3%)	2(1.3%)	37(2.2%)	
Prostrate	7(0.5%)	1(0.7%)	8(0.5%)	
Renal	7(0.5%)	2(1.3%)	9(0.5%)	
Bladder	2(0.1%)	0(0%)	2(0.1%)	
Ovarian	2(0.1%)	0(0%)	2(0.1%)	
Cervical	0(0%)	2(1.3%)	2(0.1%)	
Endometrial	6(0.4%)	0(0%)	6(0.4%)	
Myeloma	5(0.3%)	0(0%)	5(0.3%)	
Non hodgkins lymphoma	4(0.3%)	0(0%)	4(0.2%)	
Sarcoma	4(0.3%)	1(0.7%)	5(0.3%)	
Leukemia	3(0.2%)	0(0%)	3(0.2%)	
Basal cell	2(0.1%)	1(0.7%)	3(0.2%)	
Nasopharyngeal cancer	2(0.1%)	0(0%)	2(0.1%)	
Squamous cell cancer of maxillary sinus	1(0.1%)	0(0%)	1(0.1%)	

Table III. Dietary status of the patients at the time of hypoglycemic event

	Without hypoglycemia	With hypoglycemia
Dietary status	n=1,526	n=150
Oral diet	1,456(95.45)	126(84%)
Tube feeding	40(2.6%)	12(8%)
Nothing per orem	31(2%)	12(8%)

Table IV. Type of pharmacologic therapy at the time of hypoglycemic event

Type of pharmacologic therapy	Without hypoglycemia n=1,526	With hypoglycemia n=150	*p*-value
Composite			
Oral therapy	921[60.4%]	51[34%]	<0.001
Combination of oral and insulin	252[16.5%]	38[25.3%]	0.006
Insulin	184[12.1%]	52[34.7%]	<0.001
Specific types			
Oral monotherapy			
With sulfonylurea	83(5.4%)	7(4.7%)	0.303
Without sulfonylurea	331(21.7%)	7(4.7%)	<0.001
Multiple oral therapy			
With sulfonylurea	260(17%)	29(19.3%)	0.141
Without sulfonylurea	247(16.2%)	8(5.3%)	0.001
Combination of insulin and oral therapy			
With sulfonylurea	61 (4%)	12(8%)	0.034
Basal insulin only	43(2.8%)	8(5.3%)	0.061
Basal-bolus (rapid-acting insulin)	7(0.5%)	2(1.3%)	0.119
Basal-bolus short-acting insulin	0(0%)	0(0%)	0.000
Premix analogue insulin	10(0.7%)	2(1.3%)	0.156
Premix human insulin	3(0.2%)	0(0%)	0.244
without Sulfonylurea	191(12.5%)	26(17.3%)	0.085
Basal insulin only	60(3.9%)	9(6%)	0.069
Basal-bolus (rapid-acting insulin)	38(2.5%)	6(4%)	0.136
Basal-bolus short-acting insulin	5(0.3%)	0(0%)	0.216
Premix analogue insulin	65(4.3%)	7(4.7%)	0.364
Premix human insulin	27(1.8%)	7(4.7%)	0.02
Insulin alone			
Basal insulin only	28(1.8%)	4(2.7%)	0.231
Basal-bolus (rapid-acting insulin)	60(3.9%)	17(11.3%)	<0.001
Basal-bolus short-acting insulin	2(0.1%)	1(0.7%)	0.089
Premix analogue insulin	48(3.1%)	8(5.3%)	0.07
Premix human insulin	32(2.1%)	11(7.3%)	<0.001
Rapid-acting insulin infusion	2(0.1%)	5(3.3%)	<0.001
Short-acting insulin infusion	4(0.3%)	2(1.3%)	0.037
Rapid-acting insulin rescue dose	3(0.2%)	3(2%)	0.001
Short-acting insulin rescue dose	5(0.3%)	1(0.7%)	0.284

have significant hypoglycemia events. There were 124 cases (82.7%) of hypoglycemia recorded in the non-ICU ward but only 26 cases (17.3%) were noted in the ICU ward.

Among 150 (8.9%,n=1,676 census) patients with hypoglycemia, one (0.7%) patient developed cerebrovascular disease, one (0.7%) developed nonfatal myocardial infarction, while the other had congestive heart failure (0.7%). Meanwhile, mortality rate of those who experienced hypoglycemia was 4.7%.

Discussion

This is the first local cross-sectional study on the incidence of inpatient hypoglycemia and its associated risk factors.

The rate of hypoglycemia among patients with DM in this study was 8.9%. There were varied results from previous studies with the same cut off point of <70 mg/dL of blood glucose. One retrospective study of patients admitted to

the general wards of an academic medical center showed an incidence of 10.5%.[12] Another study[2] involving admitted patients in both medical and surgical wards showed an incidence of 28.6%, while an Asian study[7] showed lower value of 1.29%. A retrospective cohort study[4] but with a lower cut point of <50 mg/dL, among hospitalized patients in a general ward, reported a 7.7% incidence.

In this study, hypoglycemia cases were classified as non-severe (88%) and severe (12%). In the Asian study, only 0.29% presented with blood glucose ≤2.8 mmol/L (≤50 mg/dL).[7] Comparing our result to a report done in a university hospital in the United States, severe hypoglycemia with blood glucose of <40 mg/dL ranged at three to 11%.[9] In another review of patients admitted to ICU, 1.9% had severe hypoglycemia (<40mg/dL).[12] The slightly higher result in our study may be due to a higher cut point of <50 mg/dL. An accurate comparison of hypoglycemia occurrences among these studies indeed would be difficult due to the different criteria employed in each study.

Hypoglycemia is a common problem in old people with DM.[16] The vulnerability of the elderly to severe hypoglycemia may be partially related to a progressive age-related decrease in β-adrenergic receptor function and a high number of clinical complications and comorbidities.[12] Indeed, the older patients of >65 years old in this study were observed to have more hypoglycemia events (52.7% vs 36.2%, $p<0.001$) than the younger age group. In a different study[2], patients aged ≥75 years were experiencing more hypoglycemia episodes (60% vs 45.2%, $p<0.01$). The predominance of older patients (>65 years old) and female gender developing hypoglycemia were also noted in the study of Quilliam.[17] The van Staa study also demonstrated a higher rate of hypoglycemia in women as compared with men.[17] This was not however detected in our study since there was equal distribution of hypoglycemia episodes in both genders. In other studies, sex did not also predispose to hypoglycemia.[18]

We have observed that there was a greater proportion of patients who had normal BMI who experienced hypoglycemia while those in the obese category were at lowest risk. Low BMI increased the risk of severe hypoglycemia significantly in one study.[19] Obesity, however, was inversely related with the risk of developing hypoglycemia, probably due to increased insulin resistance and poorer DM control as seen in one study.[18]

The mean duration of DM diagnosis was 8.56 years ± 10.34 years. In another study, patients with diabetes duration of >10 years were more likely to report hypoglycemia (13.9%) compared with those with shorter diabetes duration (8.3%).[20] Older patients with longer duration of diagnosed DM denoting insulin deficiency are at high risk for iatrogenic hypoglycemia.[1,12]

Intensive glucose control strategies implemented in randomized control trial settings in patients with type 2 DM resulted in lower HbA1c and were associated with an increased risk of hypoglycemia. Patients achieving near-normal glycemia (HbA1c <6%) and those who were poorly controlled (HbA1c ≥9) appeared to be at highest risk for severe hypoglycemia.[20] With the present advocacy that HbA1c goals should be individualized, we divided our population into the older age group (≥65 years old) and the younger age group (<65 years old) and identified hypoglycemia events in the different categories. Consistent with the study of Lipska et al20, it was noted in our study that in the younger group, those with HbA1c ≥8.1% had higher rate of hypoglycemia (20%) and the lowest category (HbA1c <7.0%) also had a significant rate of episodes (10%). In the older group, however, only those with an HbA1c of <8% showed higher risk for hypoglycemia (20.7%). The occurrence of hypoglycemia in those with low HbA1c levels could be a result of intensive treatment. The higher frequency noted among the younger group with elevated HbA1c could be due to a mismatch of intensive treatment and abrupt change of diet in the hospital.

Studies have identified advanced age, malnutrition, active cancer, end-stage renal disease, liver disease, and congestive heart failure, as contributors to hypoglycemia risk.[21] Renal failure has been identified as an independent risk factor for hypoglycemia in two studies.[17,18] The following comorbidities were noted in our study which put patients at risk for hypoglycemia: stage III, IV, V kidney disease (32.7% vs 25.1%, $p=0.043$, 12% vs 5.5%, $p=0.002$, 12% vs 4.1%, $p<0.001$, respectively) cardiovascular disease (62.7% vs 48.6%, $p<0.001$), , and congestive heart failure (8.7% vs 4.4%, $p=0.009$). In another study, they have identified end-stage renal disease (16.8% vs 8.8%, $p<0.01$), peripheral vascular disease (27.6% vs 19.4%, $p=0.02$), and dementia (19.5% vs 11.6%, $p<0.01$) as common comorbidities seen in patients with hypoglycemia.[2] However, in one review, complications of DM and other comorbidities, GFR, liver function test abnormalities were not associated with a change in risk for a hypoglycemic episode.[4] The different population studies among these studies may have contributed to varied results. A majority of our patients included in the study was on regular diet which resulted to a higher recorded rate of hypoglycemia (84%). Lower rates were noted among those on tube feeding (eight percent) and on NPO status (eight percent). Among those12 patients who had hypoglycemia events while they were on NPO status, seven patients were in preparation for a procedure (e.g. blood extraction for lipid panel, ultrasound of the abdomen, esophagogastroduodenoscopy, colonoscopy, surgery, etc.), while five were in critical condition thus diet was withheld. Most of them did not receive any hypoglycemic agents, except for three who were on insulin infusion, one was given a rescue of a subcutaneous rapid-acting analogue dose, and one was given a sulfonylurea. This common error may

be corrected by either scheduling patients first thing in the morning or after a meal, reviewing patient's medications regularly, monitoring of blood glucose intensively when placed on NPO and/or on insulin infusion, monitoring blood glucose before the patient leaves the unit for the procedure, and giving supplemental carbohydrates should blood glucose are low or expected to decrease.[13] We also noted that patients on tube feeding (whether on NGT or PEG tubes) had significant hypoglycemia rates.

Therapeutic hyperinsulinemia, whether by treatment with an insulin secretagogue or with insulin, is a prerequisite for the development of iatrogenic hypoglycemia.[1] In this study, being on oral therapy alone recorded a low incidence of hypoglycemia (34% vs 60.4%, $p<0.001$). This was consistent with one study done in North Carolina (24% vs 44%, $p<0.0001$).2 Monotherapy with a sulfonylurea (4.7% vs 5.4%, $p=0.303$) or another oral agent (4.7% vs 21.7%) did not increase the incidence of hypoglycaemia in this study. This contrasted with a study on the burden of sulfonylurea-related hypoglycemia in United Kingdom in which it observed that sulfonylurea caused 31.8% of all hypoglycemia readings.[6] Notably, oral therapy without the use of sulfonylurea showed a lesser risk of hypoglycemia in our study.

Being on insulin therapy caused more events of hypoglycemia during hospital stay. Combination with oral agents (25.3% vs 16.5%, $p=0.006$) or used alone (34.7% vs 12.1%, $p<0.001$) caused most of the recorded hypoglycemia events in this study. Ghazi observed the same in his study that patients who used insulin, whether in combination with oral therapy (14% vs 9.5%, $p<0.0001$) or used alone (51.6% vs 23.5%, $p<0.0001$) had more hypoglycemia episodes.[2] In fact, he observed that the use of either long- or intermediate-acting insulin (76.7% vs 36.8%, $p<0.0001$) and insulin infusion (5.9% vs 2.0%, $p<0.01$) were common causes of hypoglycemia.[2] In addition, a study by Garg et al. exhibited the increased incidence of hypoglycemia among insulin treated group (41.3%) than in the non-insulin treated group (16.3%) with $p<0.0001$.[11]

The non-ICU ward recorded more episodes of hypoglycemia (82.7%) than the ICU ward. The greater number of admission and fast turnover of patients in this ward may have contributed to this figure. This number was comparable with previous studies where a prevalence of five to 32% in a non-ICU setting was noted among patients treated with subcutaneous insulin.[22] In contrast to the study of Swanson et al.[5] which analyzed measurements from the largest number of US hospitals, the prevalence of hypoglycemia was 6.3% in ICU patients and 5.7% in non-ICU patients.

We have detected that only few patients had significant outcomes after the hypoglycemia event. There were seven patients who died during their hospital stay and were all at a grave state since admission. Five of them were resuscitated upon arrival in the emergency room, while two of them were in septic shock since admission. Four of them developed severe hypoglycemia, of which three were on continuous insulin infusion and only one was on NPO status. According to Turchin[4], inpatient mortality was 2.96% for patients who had at least one hypoglycemic episode during the hospital stay. In-patient mortality rate increased progressively from 1.9% for patients with lowest blood glucose of >39 mg/dL to 8.2% for those with lowest glucose of <30 mg/dL.[4] Though the categorization of severe and non-severe hypoglycemia in this study varies with that of Turchin, nevertheless, a strong relationship between increased risk for mortality and low blood sugar levels (<50 mg/dL) was also noted in our study.

This study has several limitations. Though the total study population was quite large, a longer timeframe (ex. ≥one year) would have identified the true incidence of hypoglycemia in our locality. The frequency of blood glucose determination which was not uniform across all patients could have missed some episodes of asymptomatic hypoglycemia relevant to the determination of hypoglycemia unawareness which is common among the elderly population. Additionally, the degree of distribution of hypoglycemia was based only on numerical blood glucose values. Determining the symptoms of hypoglycemia would have added to the clinical relevance of the study. Also, some patients did not have complete data (e.g. HbA1c or creatinine within one month of admission) and their determination was limited to the discretion of the attending physician. Other factors that were not studied here include the dose of medications during the hypoglycemia event, review of possible overlapping medications (e.g. combination of gliclazide and glimepiride), correlation of hemoglobin and HbA1c values, relationship of severe hypoglycemia to inpatient mortality. Finally, the generalizability of this single-center study may be limited.

Conclusion

In this study, we have focused on the total census patients with type 2 DM, excluding the minors and the pregnant patients. The incidence of hypoglycemia of 8.9%, though predominantly of the non-severe type, is indeed a realization that this should be addressed aggressively to decrease the burden of DM management. The elderly, longer duration of DM diagnosis, comorbidities like moderate to end-stage kidney disease, cardiovascular disease and congestive heart failure, and the use of insulin have been identified as factors for hypoglycemia. These patients should have intensive monitoring of blood glucose and regular review of medications. The recorded consequences of hypoglycemia in our study were not relevant, except for the mortality rate of 4.7%. It is still noteworthy that these events may happen because of hypoglycemia. Lastly, with these findings, though not generalizable in our country, physicians will now be vigilant in preventing hypoglycemia. This would greatly help our patients in their struggle against DM.

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