Comparative Analysis of Hypoglycemia Trends Between Patients with Diabetes and without in a Tertiary Care Hospital, Oman

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Abstract

Objective: Hypoglycemia is one of the most common causes for emergency department visits. Here we conducted a retrospective cross-sectional investigation to estimate the hypoglycemia incidence and trends in the Emergency Department (ED) of Sultan Qaboos University Hospital (SQUH) in the period prior to Coronavirus disease 2019 (COVID-19) pandemic.

Methods: We reviewed hospital records of all adult patients (Age ≥15 years) who were admitted to the ED with hypoglycemia (random blood glucose level (RBS) of ≤3.9 mmol/L) between January 2010 and January 2017.

Results: A total of 242 patients (n= 242) were admitted to ED with hypoglycemia. The incidence of hypoglycemia showed an increase, primarily from 2011 (3.31/10,000) to 2017 (6.33/10,000). In hypoglycemia patients, abnormal heart rate was significantly higher among patients without diabetes compared to patients with diabetes (*P*-value= 0.010). Moreover, the following aetiologies were significantly higher among patients without diabetes compared to patients with diabetes: liver disease, liver cirrhosis, malignancies, drugs/ toxins, and infection/Sepsis. Whereas, cerebrovascular diseases were significantly higher among patients with diabetes (*P*-value< 0.05 trend for all). In terms of hypoglycemia management, intravenous dextrose was used significantly more for patients with diabetes compared to those without diabetes (P-value= 0.015). In the study cohort, glucagon was only used on one patient.

Conclusion: The incidence of hypoglycemia at the ED of SQUH increased during the study period. Intravenous dextrose was the primary management approach, whereas, glucagon was the least used. Further investigation is required to decipher the current hypoglycemia trends compared to the period prior to the pandemic.

Keywords: Diabetes;Type 2 Diabetes;Hypoglycemia; Emergency Department; Glucagon.

Introduction

Hypoglycemia is regarded as one of the leading causes for Emergency Department (ED) visits worldwide.[1] It is one of the complications associated with diabetes mellitus (DM). The expected increase in DM prevalence worldwide

(from 463 million cases in 2019 to 578 million cases by 2030), is anticipated to cause a proportional increase in hypoglycemia's incidence.[1,2]

The American Diabetes Association (ADA) defines hypoglycemia as an abnormally low random blood sugar (RBS) levels of ≤ 3.9 mmol/L (70 mg/dL).[3] However, this threshold can slightly vary among patients depending on their clinical conditions. For instance, patients with poorly controlled DM may experience symptoms of hypoglycemia at a higher glucose level compared to those with tightly controlled DM.[4-6] Moreover, young patients newly diagnosed with DM are likely to experience symptoms of hypoglycemia at a higher plasma glucose level.[4-6]

Hypoglycemia primarily develops in patients with DM undergoing treatment with insulin or sulfonylureas due to improper administration at high dose or incorrect timing related to meals intake.[7] Symptoms of hypoglycemia are categorized into two types: neurogenic, due to a rapid drop in glucose levels, or neuroglycopenic, due to insufficient glucose availability to the central nervous system (CNS). The most common symptoms associated with neurogenic hypoglycemia are sweating, palpitation, tremor, anxiety, and paraesthesia, whereas, neuroglycopenic symptoms manifest in impaired cognition, seizures, and coma.[2]

Hypoglycaemia is typically managed by glucose or dextrose administration.[7] Although Glucagon is considered the first-line of treatment for patients with severe hypoglycemia,[8] it remains underappreciated and underused.[6] Glucagon is a polypeptide hormone produced by the alpha cells of the pancreas. It binds to glucagon receptors found throughout the body. This activates G-protein-coupled receptors, which in turn activate adenylate cyclase, resulting in an increase in cAMP levels. This process activates glycogenolysis and glucogenesis, causing an increase in blood glucose levels.[2,9,10] Currently, the availability of novel glucagon formulations such as: nasal glucagon and liquid glucagon, is expected to make a shift in the management of hypoglycemia compared to previous years.[8]

This study aims to identify the incidence of hypoglycaemia and its causes in the ED at a tertiary care hospital in Oman during the years prior to Coronavirus disease 2019 (COVID-19) pandemic. The knowledge of the pre-pandemic hypoglycemia trends may serve as a baseline for comparison with the trends at the years during and after the pandemic. Moreover, in this study we investigate the hypoglycemia treatment approaches and the use of glucagon as a treatment option during the study period (2020-2017). This may also serve as a baseline for comparison to its present use particularly with the current availability of novel glucagon formulations.

Methods

Ethical approval was obtained from the Medical & Research Ethics Committee at Sultan Qaboos University, Muscat, Oman (MERC# 1612).

This cross-sectional retrospective study was conducted on all adult patients admitted with hypoglycemia to the ED at Sultan Qaboos University Hospital (SQUH) (a tertiary care teaching hospital in Oman). The inclusion criteria for the study were: Age ≥15 years old at the time of ED arrival with random blood glucose level (RBS) of ≤3.9mmol/L (70mg/dL) in the period from January 2010 to January 2017, whereas, for the exclusion criteria: patients aged <15 years at arrival to the ED with RBS >3.9 mmol/L during the study period. Patient data were retrieved from the SQUH Track care database system. Records of n= 242 patients were included and reviewed in the study. For each subject: the demographic characteristics, presenting symptoms and signs, suspected aetiologies of hypoglycemia, and treatment approach were recorded. Cases of mortality were also recorded.

Completed data were analyzed using Statistical Package for Social Science (SPSS) version 23.0. Descriptive statistics were presented as mean ± standard deviation for continuous variables and some categorized variables. Categorized variables were analyzed with the Chi-square test and presented with numbers and percentages. P-value ≤0.05 was taken as statistical significance.

Results

We reviewed the records of n= 242 patients ≥ 15 *y*ears old admitted to the ER with hypoglycemic episodes during the period from January 2010 to January 2017. This cohort comprised of n= 116 males (47.9%) and n=126 females (52.1%). The cohort had random blood sugar (RBS, mmol/L) of (mean ±SD) 2.32±0.69. The majority of the study population had diabetes (n= 187, 77.3%), with Type-2 diabetes (T2D) being the most prevalent (n= 162, 67%) followed by Type 1 diabetes (T1D) (n= 25, 10.3%). Patients without diabetes accounted for n= 55 (22.7%) of the sample size. The RBS (mean ±SD, mmol/L) for patients with diabetes was 2.29±0.67 and for patients with no diabetes 2.43±0.78. No significant difference was observed between patients with diabetes and patients without diabetes in terms of sex (*P*-value= 0.169), marital status (*P*-value= 0.153), and Body Mass Index (BMI) (*P*-value= 1.000). In terms of smoking status, the number of non-smokers was significantly higher for patients with diabetes compared to patients without diabetes (92.5% vs. 81.8%, *P*-value= 0.011). In terms of alcohol consumption, 97.3% of patients with diabetes were non-alcohol drinkers, which is significantly higher than that observed for patients without diabetes (87.35%) (*P*-value= 0.022). (Table 1, Fig.1).

Table 1: Distribution of demographic and association between diabetic status.

Variables	Total (n=242) n (%)	Diabetes (n=187) n (%)	Non-diabetes (n=55) n (%)	p-Value
Gender *- Male*	116 (47.9)	85 (45.5)	31 (56.4)	0.169
Marital status *- Married*	223 (92.1)	175 (93.6)	48 (87.3)	0.153
BMI *– Abnormal (≥25 and < 18.5)*	75 (59.1)	61 (59.2)	14 (58.3)	1.000
Non-smokers	218 (90.1)	173 (92.5)	45 (81.8)	0.011
Non-alcoholic	230 (95.0)	182 (97.3)	48 (87.3)	0.022

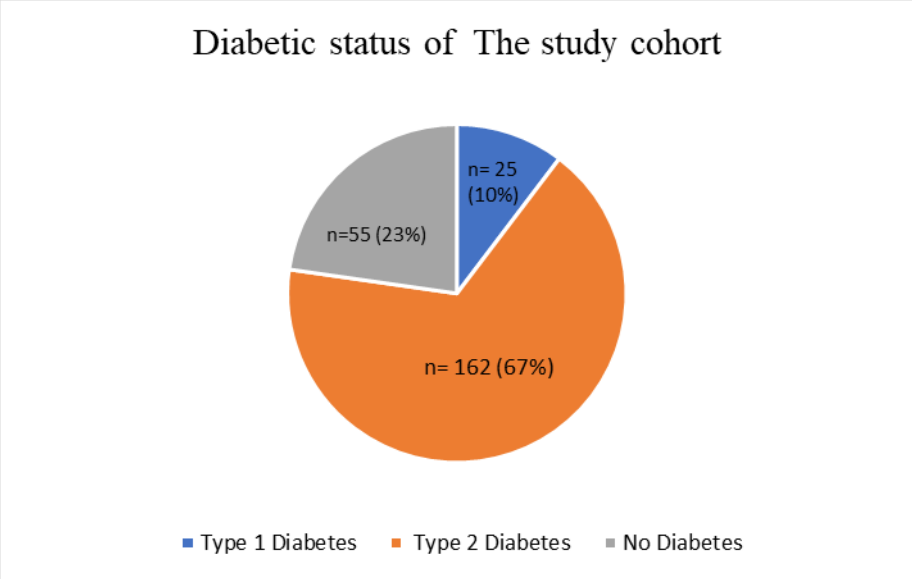

Figure 1: The diabetic status of the hypoglycemia cases in the study cohort over the period from 2010-2017.

The incidence of hypoglycemia was examined over seven years of the study period. In 2010, the incidence was 4.85 per 10,000 patients. However, in the following year, a decrease in the incidence was observed to be 3.31. From 2012-2013, the incidence remained relatively stable, with rates of 3.44 and 3.52, respectively. The incidence showed an elevation from 5.31 in 2014 to 6.25 in 2015 and continued to ascent, reaching a peak of 6.33 in 2016. This was followed by a drop in the incidence to 5.25 in 2017 (Fig. 2).

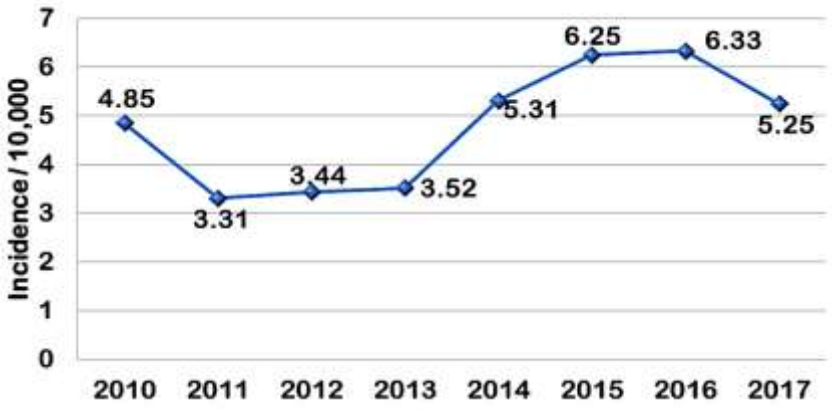

Figure 2: Incidence of hypoglycemia at Emergency Department (ED) of Sultan Qaboos University Hospital (SQUH) over the period from 2010-2017.

Presenting signs and symptoms have been evaluated for the study cohort. The most frequently observed presenting symptom for hypoglycemia was abnormal blood pressure (both Systolic (n=175, 72.3%) and diastolic (n=118, 48.8%), followed by abnormal body temperature (n=69, 28.5%) and abnormal heart rate (n=67, 27.7%). Drowsiness was reported in (n= 43, 17.9%) of patients, followed by gastrointestinal (GI) symptoms (n= 36, 15.0%). Other reported signs and symptoms, listed in descending order for frequency, included motor deficit (n= 26, 10.9%), sweating (n= 23, 9.6%), fever (n= 20, 8.3%), conscious less (n= 17, 7.1%), electrolyte imbalances (n= 6, 2.5%), palpitations (n= 4, 1.7%), seizures (n= 3, 1.3%), hypoglycemic coma (n= 2, 0.8%), anemia (n= 3, 1.3%), and altered coagulation/ bleeding (n= 3, 1.3%) (Table 2).

Table 2: Association between diabetic status and presenting symptoms, suspected etiology and intervention received.

Variables	Total (242) n (%)	Diabetes (n=187) n (%)	Non-diabetes (n=55) n (%)	p-Value
Symptoms				
Body temperature	69 (28.5)	52 (27.8)	17 (30.9)	0.734
Heart Rate	67 (27.7)	44 (23.5)	23 (41.8)	0.010
Systolic BP	175 (72.3)	145 (77.5)	30 (54.5)	0.002
Diastolic BP	118 (48.8)	94 (50.3)	24 (43.6)	0.444
Hypoglycemic Coma	2 (0.8)	2 (1.1)	-	1.000
Fever	20 (8.3)	13 (7.5)	7 (12.7)	0.175
Neutropenia	-	-	-	-
Electrolyte imbalance	6 (2.5)	5 (2.7)	1 (1.8)	1.000
GI symptoms	36 (15.0)	23 (12.4)	13 (23.6)	0.052
Anaemia	2 (0.8)	1 (0.5)	1 (1.8)	0.407
Altered INR / Coagulation / bleeding	2 (0.8)	2 (1.1)	-	1.000
Sweating	23 (9.6)	19 (10.3)	4 (7.3)	0.610
Drowsiness	43 (17.9)	30 (16.2)	13 (23.6)	0.231
Palpitations	4 (1.7)	3 (1.6)	1 (1.8)	1.000
Seizures	3 (1.3)	1 (0.5)	2 (3.6)	0.132
Conscious less	17 (7.1)	15 (8.1)	2 (3.6)	0.476
Motor deficit	26 (10.9)	20 (10.9)	6 (10.9)	1.000
Etiology				

Variables	Total (242) n (%)	Diabetes (n=187) n (%)	Non-diabetes (n=55) n (%)	p-Value
Symptoms				
Liver disease	19 (7.9)	11 (6.0)	8 (14.5)	0.049
Liver cirrhosis	10 (4.2)	4 (2.2)	6 (10.9)	0.011
Acute renal dysfunction	7 (2.9)	7 (3.8)	-	0.357
Renal dysfunction	62 (25.9)	51 (27.7)	11 (20.0)	0.295
Malignancies	12 (5.0)	6 (3.3)	6 (10.9)	0.034
Poor oral intake	57 (23.8)	43 (23.4)	14 (25.5)	0.723
Drugs / toxins	5 (2.1)	-	5 (9.1)	0.001
Infection / Sepsis	37 (15.4)	23 (12.4)	14 (25.5)	0.031
Cerebrovascular disease	152 (63.6)	131 (71.2)	21 (38.2)	<0.001
Uraemia	3 (1.3)	3 (1.6)	-	1.000
Urinary tract infection	11 (4.6)	9 (4.9)	2 (3.6)	1.000
Pneumonia	11 (4.6)	8 (4.3)	3 (5.5)	0.719
Intervention received at EMD				
Juice or honey	58 (24.3)	46 (25.0)	12 (21.8)	0.722
Glucagon	1 (0.4)	-	1 (1.8)	0.230
Glucose gel	4 (1.7)	3 (1.6)	1 (1.8)	1.000
Bolus glucose	23 (9.6)	20 (10.9)	3 (5.5)	0.303
Intravenous dextrose	211 (88.3)	168 (91.3)	43 (78.2)	0.015
Death	4 (1.7)	2 (1.1)	2 (3.6)	0.226

Comparisons between patients with diabetes and patients without diabetes revealed that abnormal heart rate was significantly higher among patients without diabetes (n=23, 41.8%) compared to patients with diabetes (n=44, 23.5%) (*P*-value= 0.010). Moreover, a significant difference was also observed in abnormal Systolic blood pressure, in which it was significantly higher among patients with diabetes (n=145, 77.5%) compared to patients without diabetes (n=30, 54.5%) (*P*-value= 0.010) (Table. 2).

The etiology of hypoglycemia in patients admitted to the ER was determined based the patients underlying diseases or comorbidities that may contribute to thee hypoglycemic episode. The most frequently observed aetiologies for hypoglycemia in the study cohort were: cerebrovascular disease (n=152, 63.6%), renal dysfunction (n=62, 25.9%), poor oral intake (n=57, 23.8%), and infection/ sepsis (n=37, 15.4%) (Table. 2).

Comparisons between patients with diabetes and patients without diabetes revealed that the following aetiologies were significantly higher among patients without diabetes compared to patients with diabetes: liver disease (n= 8 (4.5%) vs. n= 11 (6.0%), *P*-value= 0.049), liver cirrhosis (n=6 (10.9%) vs. n=4 (2.2%), *P*-value= 0.011), malignancies (n=6 (10.9%) vs. n=6 (3.3%), *P*-value= 0.034), drugs/ toxins (n=5 (9.1%) vs. n=0 (0.0%), *P*-value= 0.001), and infection/ Sepsis (n=14 (25.5%) vs. n=23 (12.4%), *P*-value= 0.031). However, cerebrovascular diseases were significantly higher among patients with diabetes n=131 (71.2%) compared to patients without diabetes n=21 (38.2%), *P*-value< 0.001) (Table. 2).

Investigation of interventions and treatments for hypoglycemia employed on the study cohort revealed the use of five different approaches: intravenous dextrose as the most frequently used approach (n= 211, 88.3%), followed by juice or honey consumption (n= 58, 24.3%), bolus glucose (n= 23, 9.6%), and Glucose gel (n= 4, 1.7%). Glucagon was the least-used intervention approach, as it was used only in one patient out of the 242 patients in the study cohort (n= 1, 0.4%).

Comparisons between patients with diabetes and patients without diabetes revealed that intravenous dextrose was used significantly more for patients with diabetes (n= 168, 91.3%) than for patients without diabetes (n= 43, 78.2%, *P*-value= 0.015).

Although in the study cohort no mortality was attributed to hypoglycemia, four death cases were reported but these were attributed to pre-existing comorbidities unrelated to the hypoglycemia: metastatic hepatocellular carcinoma, sepsis septic shock, hepatitis C liver cirrhosis and sepsis and low ejection fraction heart failure.

Discussion

Hypoglycaemia is one of the frequently presented cases to EDs, particularly for diabetic cases. The severity of hypoglycemic episodes can range from mild nausea to profound neurological impairment.[7] For patients with T1D, hypoglycemia has been linked to a mortality rate of 2-6%.[11,12] Early identification of hypoglycemia and prompt interventions are crucial to minimize hypoglycemia's adverse consequences. This study aimed to determine the incidence of hypoglycemia in ED at SQUH (a tertiary care teaching hospital in Oman) and its presenting symptoms, causes, and treatment approaches during the years prior to the Coronavirus disease 2019 (COVID-19) pandemic. During COVID-19 pandemic, risk of hypoglycemia in patients with T2DM increased.[13] This increase was attributed to several factors such as limited access to health care services and the use of use of certain medications such as hydroxychloroquine (HCQ).[14] Moreover, COVID-19 virus effects on the immune system may trigger episodes of hypoglycemia.[15] Therefore, results from this study of years prior to the pandemic may serve as a base line for comparison with the hypoglycemia trends in years during and after the pandemic.

Hypoglycemia has been previously reported to be associated with various heart rate abnormalities including: ventricular tachycardia, atrial fibrillation, ventricular arrhythmias, and bradycardia.[16,17] The low blood pressure during hypoglycemia is compensated with the secretion of epinephrine resulting in an increased heart rate (tachycardia) in order to supply more glucose to the tissues.[17] Moreover, the low blood pressure during hypoglycemia can disrupt the normal hearts' electrical activity resulting in atrial fibrillation or ventricular arrhythmias.[18] In severe cases of hypoglycemia, due to the limited glucose delivery to the vital organs such as the brain, the heart's ability to sustain a normal heart rate becomes impaired causing bradycardia (a dangerously slow heart rate).[19]

In our study cohort, abnormal heart rate was significantly higher among patients without diabetes compared to patients with diabetes (P=0.010). This could be due to the significantly higher aetiologies reported for the patients without diabetes compared to the patients with diabetes such as: liver disease (14.5% vs. 6.0%, P=0.049), liver cirrhosis (10.9% vs. 2.2% P=0.011), malignancies (10.9% vs. 3.3%, P=0.034), Drugs / toxins (9.1% vs. 0.0%, P=0.001), and Infection / Sepsis (25.5% vs. 12.4%, P=0.031).

Vascular complications are one of the long-term complications for hypoglycemia.[20] Moreover, recurrent episodes of hypoglycemia in patients with diabetes poses a great cardiovascular risk as a result of vascular damage.[21] Hypoglycemia triggers a cascade of physiological changes such as: elevation in platelet aggregation and coagulation factors, as well as inducing inflammation that results a negative impact on vasculature.[20,21] In the study cohort, cerebrovascular diseases (CVD) were found to be significantly higher among patients with diabetes compared to patients without diabetes (71.2% vs. 38.2%, P<0.001). However, in the study cohort, the CVD condition was present independently from the hypoglycemia incidence.

The ED management of hypoglycemia depends on the severity of the condition. Various intervention approaches are used for hypoglycemia, including glucose intake in the form of juice, honey or glucose gel for mild cases and intravenous dextrose, and glucagon for sever cases.[8,22]

In our cohort, Intravenous dextrose was the most commonly used treatment approach (88.3% of all cases). Moreover, the use of intravenous dextrose was significantly higher for patients with diabetes (91.3%) compared to patients without diabetes (78.2%) (P= 0.015). Glucagon use was found to be the least employed management approach as it was used in one case only that was free from diabetes (0.4% out of the 242 cases) during the study period (2010-2017).

The use of glucagon in both clinical and non-clinical settings for hypoglycemia management remains limited despite its effectiveness and safety in restoring both blood glucose levels and consciousness.[6] Glucagon has several advantages compared to dextrose: it can be administrated without the requirement of a healthcare worker, also can be administrated subcutaneously (SC) or intramuscularly (IM).[6] A study conducted in 2020 reported a success rate of 90.6% of both trained and untrained users in administrating nasal glucagon. In addition, 7.9% of users successfully administer injectable glucagon.[23] The current availability of novel glucagon formulations such as: nasal glucagon and liquid glucagon,[8] as well as providing glucagon kits and educating parents and school nurses on its administration may aid in the future reduction of hypoglycemia incidence in ED.

This study presents the hypoglycaemia trends at the ED at a tertiary hospital in Oman during the years prior to Coronavirus disease 2019 (COVID-19) pandemic, which may be used as a baseline for comparison with the trends during and after the pandemic in terms of incidence, aetiologies and managements. Moreover, given the considerable evidence supporting the use of glucagon as a management approach for hypoglycemia, its administration should be more frequent particularly for severe cases of hypoglycemia.

Several limitations need to be considered when interpreting the findings of this study. First, the retrospective nature of the study, which may have resulted in the absence of some data. Second, the study was conducted in a single center, which limit the generalizability of the findings to other hospitals or healthcare settings. The study did not compare the effectiveness of different treatment modalities, which warrants further investigation. Finally, this study reports findings of the time period between 2010 and 2017, which might not reflect the current hypoglycemia trends, however, may serve as a baseline for comparison with the period during and post the pandemic.

Disclosure

The authors declare that they have no competing interests. This research did not receive or require any grant or funding. Also, all authors declare no conflict of interest.

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