Krishnamoorthy et al. Scr Med. 2024 May-Jun;55(3):287-96. DOI:10.5937/scriptamed55-50079

ORIGINAL ARTICLE

Clinical Characteristics and Hospitalisation Outcomes of Hypoglycaemia in Hospitalised Patients With Type 2 Diabetes Mellitus

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Abstract

Background/Aim: Strict glycaemic control delays the onset as well the progression of diabetes related microvascular complications. The major roadblock in achieving the target glycated haemoglobin (HbA_1c) and blood glucose levels is hypoglycaemia. The aim of this study was to assess the clinical characteristics and outcomes of hypoglycaemia in the type 2 diabetes mellitus (T2DM) hospitalised patients.

Methods: This was an observational study done for nine months in T2DM patients who had documented hypoglycaemia (blood glucose < 70 mg/dL) during the hospital stay. T2DM patients with hypoglycaemia on admission, hypoglycaemia due to anti-diabetic drug overdose, intensive care unit (ICU) patients with hypoglycaemia were excluded from the study. Eligible patients were categorised into two groups as symptomatic and asymptomatic hypoglycaemia. Clinical features, risk factors, hospitalisation outcome were compared between the symptomatic and asymptomatic hypoglycaemia group.

Results: Two hundred patients were enrolled in this study (n = 89, symptomatic group and n = 111, asymptomatic hypoglycaemia). Hypoglycaemic episode in past was significantly associated with symptomatic hypoglycaemic events during hospitalisation [34 (38.2 %) vs 27 (24.3 %)], p = 0.01. Admission blood glucose levels (mg/dL), HbA_1c (%) were significantly higher in symptomatic hypoglycaemia group [(225.93 vs 178.72, p = 0.008), (8.55 ± 2.49 vs 7.72 ± 1.82, p = 0.007)], respectively. The blood glucose level during the hypoglycaemia episode was significantly higher in patients with asymptomatic hypoglycaemia group (56.38 ± 9.51 vs 44.22 ± 11.21 mg/dL, p < 0.001). Patients with $HbA_1c \leq 6$ % were significantly higher in asymptomatic hypoglycaemia (n = 12, 10.8 % vs n = 2, 2.24 %, p = 0.02). Majority recovered fully without complications and got discharged (n = 155, 77.5 %).

Conclusion: In presented study, symptomatic hypoglycaemic patients had significantly higher admission blood glucose levels and HbA_1c %. Patients with HbA_1c < 6 % were significantly higher in asymptomatic group. Past history of hypoglycaemia was significantly associated with symptomatic hypoglycaemia during hospitalisation.

Key words: Blood glucose; Glycated haemoglobin; Hypoglycaemia; Symptoms; Type 2 diabetes mellitus.

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Citation:
Krishnamoorthy S, Pandurangan V, Varadan S, Gopalan S, Singh S RB. Clinical characteristics and hospitalisation outcomes of hypoglycaemia in hospitalised patients with type 2 diabetes mellitus. Scr Med. 2024 May-Jun;55(3):287-96.

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Received: 27 March 2024
Revision received: 29 April 2024
Accepted: 29 April 2024

Introduction

Strict glycaemic control is a major goal in treating patients with diabetes. The UK Prospective Diabetes Study (UKPDS) and The Diabetes Control and Complication Trail (DCCT) have shown reduced diabetes related microvascular complications like neuropathy, retinopathy and nephropathy with tighter blood glucose control and intensive therapy.[1, 2] Glycated haemoglobin (HbA_1c) target of less than 7 is recommended by American diabetes association (ADA). In practice, the major limiting factor in achieving desirable glycaemic control and target HbA_1c is hypoglycaemia.[3] However misconceived notion among doctors is that hypoglycaemia is uncommon in type 2 diabetes mellitus (T2DM) compared to type 1 diabetes mellitus. Early in the course of T2DM, hypoglycaemia is relatively rare as glucose counter-regulatory responses like secretion of glucagon, adrenaline is preserved. Over time with increasing duration of diabetes and beta cell failure, functional beta cell reserve decreases and there is failure of counter-regulatory responses. Occurrence of hypoglycaemic events in later course of T2DM is common.[4, 5] Moreover, recurrent episodes of hypoglycaemia cause hypoglycaemic unawareness and hypoglycaemia associated autonomic failure (HAAF).[6] Hypoglycaemic unawareness is due to attenuated adrenal response where patients may not experience the symptoms corresponding to the fall in blood glucose levels and sometimes the threshold that stimulates the response, drops below neuroglycopenia associated glucose levels. Blunted counterregulatory response and sympathoadrenal failure are components of HAAF. For the severity of hypoglycaemia, patients with HAAF have decreased epinephrine and glucagon response and subsequent development of neuroglycopenic symptoms. This sets a vicious cycle and causes sympathoadrenal failure later.

India holds second position worldwide with approximately 74-75 million people living with T2DM and projected number is 125 million by the year 2045.[7, 8] However, the data on prevalence, demographic characteristics, risk factors of hypoglycaemia in type-2 diabetic patients is inconsistent and sparse. Elderly people, patients with multiple comorbidities are frequently prone for hypoglycaemic episodes. Hypoglycaemia is considered as a significant risk factor for adverse cardiovascular events like myocardial infarction, arrythmias.[9] Fear of hypoglycaemia in patients and treating doctors naturally drives towards less intensified regimen resulting in sub-optimal glycaemic control. Despite all the threats posed by hypoglycaemia, still it remains a complication overlooked in clinical practice. Sulphonylureas drugs and insulin are known to cause hypoglycaemia. Risk factors of hypoglycaemia include elderly patients, co-prescription of certain antibiotics like fluroquinolones, HbA_1c levels. Hence, this study intended to study the clinical features, risk factors of in-patient hypoglycaemic events and its outcome in hospitalised patients with T2DM. It was intended to assess whether admission blood glucose, HbA_1c, antidiabetic drugs used, blood glucose levels during the hypoglycaemic event had any significant association between symptomatic and asymptomatic group.

The aim of the study was to compare the clinical characteristics, risk factors, glycaemic status, complications, length of stay and outcome of in-patient hypoglycaemia between the groups of symptomatic and asymptomatic hypoglycaemia patients with T2DM.

Methods

This was a prospective observational study done for a period of nine months between November 2020 and July 2021. Study was conducted in a tertiary care hospital in Southern India. Patients were enrolled from general medicine wards. Patients with T2DM above 18 years who were admitted in medical wards and subsequently during hospital stay had hypoglycaemia (blood glucose level < 70 mg/dL) were included in this study. T2DM patients who had hypoglycaemia after hospitalisation were enrolled. Non-inclusion criteria were: i) patients less than 18 years of age, ii) non-diabetic patient, whose capillary blood glucose (CBG) < 70 mg/dL, iii) pregnant patients, v) patients admitted with overdose of glucose lowering drugs, vi) patients who did not give consent for the study, vii) T2DM patients with hypoglycaemia on admission, viii) T2DM patients with sepsis who had hypoglycaemia on arrival to emergency room.

Informed consent was taken from all the participants prior to the study. Institutional ethics committee (IEC) approval was obtained and

study followed the ethical standards for human subjects. Study was conducted in patients whose bedside capillary blood glucose (CBG) was < 70 mg/dL at any point of time during hospitalisation. The nursing staff were instructed to immediately notify patients with a blood glucose < 70 mg/dL by point of care testing. These patients were approached after reviewing medical records and confirming the diagnosis of diabetes. Patient's symptoms and signs during hypoglycaemic episodes were noted. Patients were categorised into two group as symptomatic and asymptomatic hypoglycaemia. Each patient was included only once in the study and symptoms were collected during the first hypoglycaemia episode. Only the first hypoglycaemic episode was included in this study and detailed information of study patients including age, sex, duration of diabetes, risk factors of hypoglycaemia (*nil per os*, decreased food intake, use of fluroquinolone, vomiting, kidney disease, liver disease and use of beta blockers), prior history of hypoglycaemia, blood glucose value during hypoglycaemic episode and treatment regimen were recorded using a standard proforma. HbA_1c, blood glucose value on admission, serum electrolytes (sodium, potassium, chloride, bicarbonate), renal function tests, serum albumin levels, the total leucocyte count done on admission were noted. Patients were followed up until discharge and the outcomes studied were duration of stay in the hospital, any adverse cardiovascular events (arrythmias, acute coronary syndrome or heart failure), nosocomial infections, acute kidney injury and mortality. Clinical characteristics, admission blood glucose, HbA_1c, CBG during the episodes and the outcomes studied were compared between the two groups (symptomatic and asymptomatic hypoglycaemia).

Symptomatic hypoglycaemia was defined as an event during which typical symptoms of hypoglycaemia were accompanied by a measured glucose concentration of ≤ 70 mg/dL. Asymptomatic hypoglycaemia was defined as an event with a measured glucose concentration of ≤ 70 mg/dl without the symptoms of hypoglycaemia. Severe hypoglycaemia was defined as measured glucose concentration < 40 mg/dL.[10] Adrenergic symptoms included sweating, anxiety, trembling, dry mouth, hand coldness, palpitations, nausea and increased appetite. Neurological symptoms were confusion, blurred vision, headache, slurred speech, numbness around lips.

Statistical analysis

Parameters were expressed as either number (percentage) or mean (standard deviation - SD) as appropriate. Descriptive data were expressed as frequency and percentage analysis for categorical variables, mean and SD for continuous variables. For continuous variables, depending on normality of data, Student's t-tests or non-parametric Wilcoxon tests were used to compare between the groups with symptomatic and asymptomatic hypoglycaemia. For discrete variables, χ^2 tests or Fisher's exact tests was used. Statistical significance was set at $p < 0.05$. Statistical analysis was done using *MEDCALC* software 2021 version.

Results

This study included a total of 200 patients with T2DM who developed hypoglycaemia during hospitalisation. Out of 200, 111 (55.5 %) patients did not experience any symptoms during hypoglycaemia episode (asymptomatic group) and 89 (45.5 %) patients were symptomatic during the episode. Fifteen percent of patients had hypoglycaemia in ICU (n = 30) and 85 % (n = 170) of patients had hypoglycaemia in wards.

The age group most commonly affected was found to be between 55-64 years in both symptomatic (n = 35, 39.3 %) and asymptomatic (n = 34, 30.6 %) group. Hypoglycaemic event occurred predominantly in patients aged more than 55 years in symptomatic (n = 64, 71.8 %) and asymptomatic group (n = 67, 60.3 %). Symptomatic patients were older than asymptomatic group, though not statistically significant (60.23 ± 11.74 vs 56.61 ± 14.69 years of age), p = 0.054. Table 1 shows the baseline characteristics of study patients. Age, gender, out-patient treatment had no significant difference between the symptomatic group and asymptomatic group.

Patients with diabetes duration of 1-5 years had higher episodes of asymptomatic hypoglycaemia compared to symptomatic group [31 (27.9 %) vs 12 (13.5 %)] which was found to be significant (p = 0.04). Patients with hypoglycaemic episode previously was found to have significantly higher symptomatic hypoglycaemic events during hospital stay [34 (38.2 %) vs 27 (24.3 %)], p = 0.01.

Table 1: Socio-demographic and clinical characteristics of patients

N	Parameter	Symptomatic group (N = 89)	Asymptomatic group (N = 111)	p-value
1.	**Age** (years) (Mean ± SD)	60.23 ± 11.74	56.61 ± 14.69	0.054
2.	**Gender, N (%)**			
	Male	52 (58.0 %)	62 (56.0 %)	0.770
	Female	37 (42.0 %)	49 (44.0 %)	
3.	**Duration of diabetes** (years) (Mean ± SD)	10.96 ± 7.56	9.24 ± 7.04	0.098
4.	**Hypoglycaemic episode in past**			
	Present, N (%)	34 (38.2 %)	27 (24.3 %)	0.040
	Absent, N (%)	55 (61.8 %)	84 (75.7 %)	
5.	**Treatment details, N (%)**			
	OHAs only	49 (55.0 %)	53 (47.7%)	0.310
	Both OHAs and insulin	21 (23.5 %)	26 (23.4%)	0.980
	Insulin only	8 (9.0 %)	19 (17.1%)	0.090
6.	**Admission blood glucose** (mg/dL) (Mean ± SD)	225.93 ± 139.02	178.72 ± 94.76	0.008
7.	**HbA_1c** (%) (Mean ± SD)	8.55 ± 2.49	7.72 ± 1.82	0.007
8.	**BUN** (mg/dL) (Mean ± SD)	19.04 ± 14.16	16.45 ± 12.16	0.160
9.	**Serum creatinine** (mg/dL) (Mean ± SD)	1.25 ± 0.94	1.17 ± 0.96	0.550
10.	**Serum albumin** (g/dL) (Mean ± SD)	3.22 ± 0.61	3.21 ± 0.68	0.910

Descriptive data were expressed as N (%) for categorical variables, mean and standard deviation (SD) for continuous variables; p value < 0.05 was considered statistically significant; OHA: oral hypoglycaemic agent; BUN: blood urea nitrogen;

Table 2: Risk factors associated with hypoglycaemia

N	Risk factors	Symptomatic group (N = 89)	Asymptomatic group (N = 111)
1.	Reduced food intake than usual, N (%)	20 (22.5 %)	20 (22.5 %)
2.	*Nil per os* (NPO), N (%)	19 (21.3 %)	19 (21.3 %)
3.	Prior renal disease, N (%)	18 (20.2 %)	18 (20.2 %)
4.	Prior liver disease, N (%)	9 (10.1 %)	9 (10.1 %)
5.	History of vomiting, N (%)	11 (12.4 %)	11 (12.4 %)
6.	Antibiotic use, N (%)	27 (30.3 %)	27 (30.3 %)
7.	Use of β-blockers, N (%)	15 (16.9 %)	15 (16.9 %)

*Data were expressed as N (%); p value < 0.05 was considered statistically significant. *Patients who were on NPO for upper gastrointestinal endoscopy, colonoscopy or ultrasonography of abdomen during the episode of hypoglycaemia;*

The observed risk factors associated with hypoglycaemia in study included decreased food intake than usual, *nil per os* (NPO), vomiting episodes, prior renal disease, underlying liver disease, use of antibiotics (any fluroquinolone), infections and history of beta blockers intake. Table 2 shows risk factors associated with hypoglycaemic episode.

Antibiotic intake was found to be slightly more in asymptomatic group (n = 36, 32.4 %) than symptomatic group (n = 27, 30.3 %). More patients in asymptomatic group (n = 30, 27 %) were on beta blockers compared to symptomatic group (n = 15, 16.9 %) though association was not statistically significant (p = 0.09). In symptomatic patients (n = 89), adrenergic symptoms were experienced by 39 (43.8 %), 34 (38.2 %) had pure neuroglycopenic symptoms and 16 (18.0 %) had both adrenergic as well as neuroglycopenic symptoms. The most common adrenergic symptom observed was sweating (n = 40, 44.9 %). The most common neuroglycopenic symptom observed was drowsiness (n = 36, 40.4 %). Other adrenergic symptoms experienced by patients included palpitations (n = 23), anxiety (n = 20), trembling of hands (n = 17), increased appetite (n = 16) and dry mouth (n = 2) as shown in Figure 1. Neuroglycopenic symptoms observed were confusion (n = 16), blurring of vision (n = 14), seizures (n = 10), slurred speech (n = 8) and perioral numbness (n = 4). Figure 2 shows neuroglycopenic symptoms.

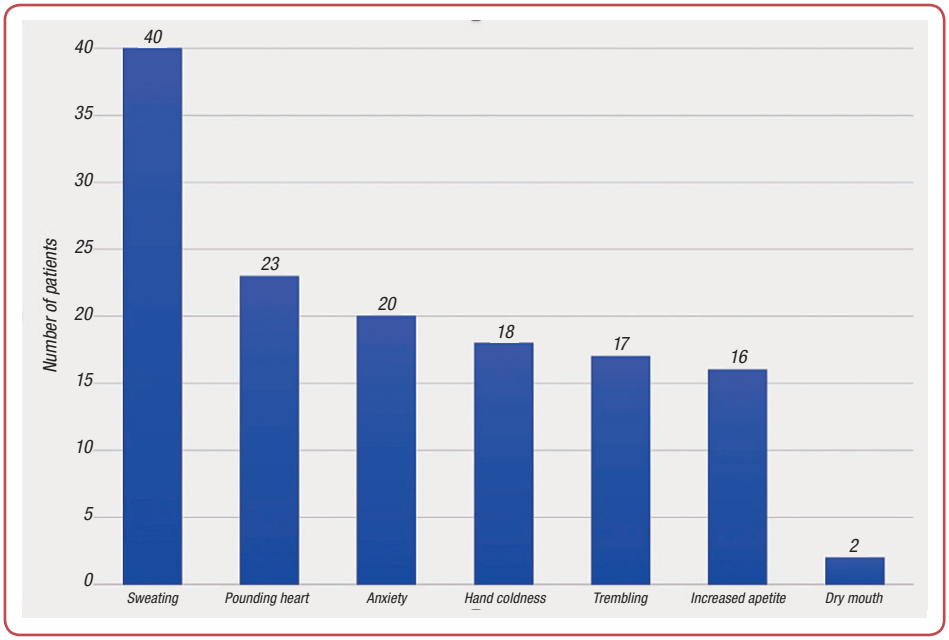

Figure 1: Adrenergic symptoms in patients with hypoglycaemia

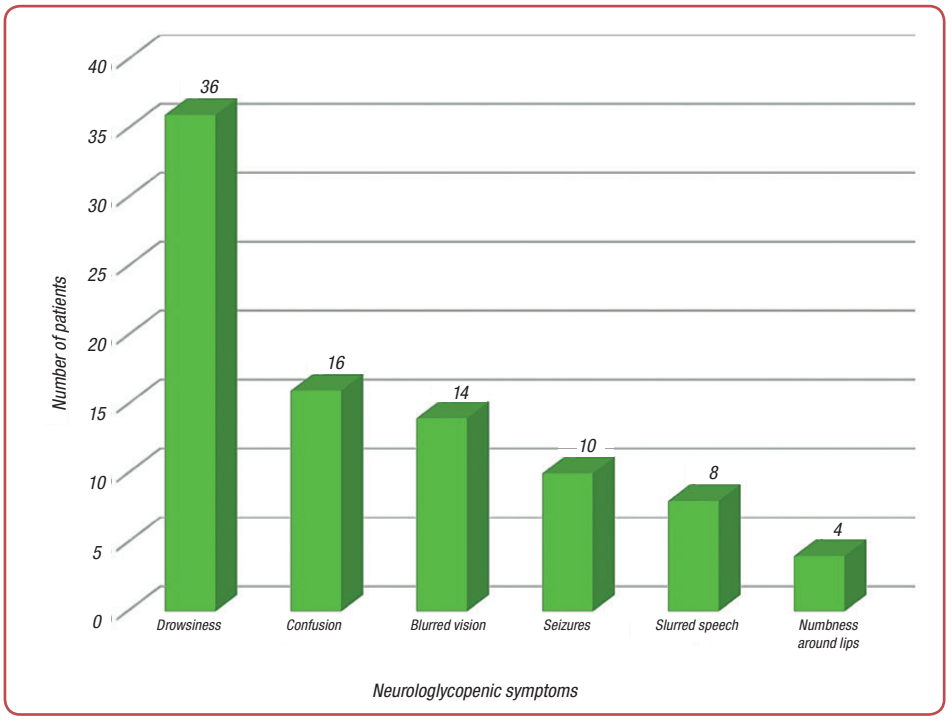

Figure 2: Neuroglycopenic symptoms in patients with hypoglycaemia

Majority in symptomatic group were only on regular insulin (n = 31, 34.8 %), whereas in asymptomatic group most were on combination of regular insulin and intermediate acting insulin (n = 45, 40.5 %) during hospital stay prior to hypoglycaemic event. It is to be noted that 9 (10.1 %) patients in symptomatic group and 8 (7.2 %) patients were not on any treatment for diabetes prior to hypoglycaemic episode as the monitored blood glucose level during stay did not require medications. There was no significant difference in the glucose lowering medication used during the hospital stay between the two groups (Table 3).

Mean admission blood glucose (mg/dL) was significantly higher in symptomatic group than asymptomatic group (225.93 vs 178.72, p = 0.008) whereas mean HbA_1c (%) was significantly lower in asymptomatic group (7.72 ± 1.82) when compared to symptomatic group (8.55 ± 2.49), p = 0.007. Admission blood glucose (mg/dL) was predominantly in the range of 101-200 mg/dL in

Table 3: Comparison of in-patient treatment among the study groups

N	Inpatient treatment	Symptomatic group (N = 89)	Asymptomatic group (N = 111)	p-value
1.	OHA only (metformin, sulphonylurea or both), N (%)	13 (14.6 %)	14 (12.6 %)	0.68
2.	Regular insulin only, N (%)	31 (34.8 %)	37 (33.3 %)	0.82
3.	Regular + neutral protamine hagedorn (NPH), N (%)	29 (32.5 %)	45 (40.5 %)	0.24
4.	OHA + regular insulin, N (%)	4 (4.5 %)	4 (3.6 %)	0.74
5.	OHA+ NPH + regular insulin, N (%)	2 (2.2 %)	1 (0.9 %)	0.43
6.	Long-acting insulin (glargine), N (%)	1 (1.1 %)	2 (1.8 %)	0.69
7.	No treatment, N (%)	9 (10.1 %)	8 (7.2 %)	0.46

Data were expressed as N (%); p value < 0.05 was considered statistically significant; OHA: oral hypoglycaemic agent;

Table 4: Blood glucose values during the hypoglycaemic episodes

N	Capillary blood glucose (CBG)	Symptomatic group (N = 89)	Asymptomatic group (N = 111)	p-value
1.	CBG (Mean ± SD)	44.22 ± 11.21	56.38 ± 9.51	< 0.0001
2.	60-69 mg/dL, N (%)	5 (5.6 %)	45 (40.5 %)	< 0.0001
3.	50-59 mg/dL, N (%)	27 (30.3 %)	44 (39.6 %)	0.1700
4.	40-49 mg/dL, N (%)	26 (29.2 %)	16 (14.4 %)	0.0100
5.	Below 40 mg/dL, N (%)	31 (34.8 %)	6 (5.4 %)	< 0.0001

Descriptive data were expressed as N (%) for categorical variables, mean and standard deviation (SD) for continuous variables; p value < 0.05 was considered statistically significant;

both symptomatic (n = 39, 43.8 %) and asymptomatic patients (n = 61, 55 %), which was found to be not significant (p = 0.11). The majority in both the groups had HbA_1c between 7.1-10.0 %. More patients (n = 12, 10.8 %) in the asymptomatic group had $HbA_1c \leq 6$ % compared to the symptomatic group (n = 2, 2.24 %), p = 0.02. Table 4 shows CBG values of study patients during the hypoglycaemic event.

In the symptomatic group, severe hypoglycaemia (CBG < 40 mg/dL) was observed in 31 patients (34.8 %) which was statistically significant (p < 0.0001) on comparison with asymptomatic group (n = 6, 5.4 %). Severe hypoglycaemia < 50 mg/dL was seen in 64 % (n = 57) of patients in the symptomatic group compared to 19.8 % (n = 22) in the asymptomatic group. Majority of patients with symptomatic hypoglycaemia had glucose value less than 40 mg/dL (n = 31, 34.8 %) during hypoglycaemia episode. Elevated serum blood urea nitrogen (BUN) was observed more in the symptomatic group (n = 29, 32.6 %) than asymptomatic group (n = 25, 22.5 %), though not significant p = 0.16. Similarly, 33.7 % of symptomatic patients with hypoglycaemia had serum creatinine more than 1.1 mg/dL compared to 27 % in asymptomatic group. No significant difference was observed in mean serum sodium (mmol/L), total leucocyte count (cells/mm^3), serum potassium (mmol/L) between symptomatic and asymptomatic group [133.79 ± 5.43 vs 135.14 ± 10.41 (p = 0.27), 11052.58 ± 5571.45 vs 11269.1 ± 5010.46 (p = 0.77), 4.2 ± 0.64 vs 4.16 ± 0.74 (p = 0.69), respectively].

Median duration of stay in the hospital for both symptomatic and asymptomatic group was eight days and there was no significant difference in length of stay between the two groups. Table 5 shows outcomes of study patients including complications.

Out of 89 symptomatic patients, 64 (72 %) improved and were discharged without any complications. Twenty-five patients (28 %) developed complications during the course in hospital, of which three patients (3.37 %) died and 22 recovered. The most common complications observed was nosocomial infection (n = 17, 19.1 %), followed by acute kidney injury (n = 12, 13.5 %), seizure (n = 10, 11.2 %) and cardiovascular events (n = 2, 2.24 %) in symptomatic group. Out of 111 asymptomatic patients, a majority of 91 (81.9 %) got improved and were discharged without any complications. Twenty patients (18 %) in asymptomatic group developed complications during the course in hospital, of which 14 (15.5 %) recovered, 2 (2.2 %) patients died and 4 (4.4 %) were lost to follow up as they were discharged against medical advice. The complications most observed were acute kidney injury (n = 18, 16.2 %), followed

Table 5: Outcomes including complications observed in patients

N	Outcome	Symptomatic group (N = 89)	Asymptomatic group (N = 111)	p-value
1.	Discharge from the hospital without any complications, N (%)	64 (71.9 %)	91 (81.9 %)	0.0900
2.	- Patients who developed complications, N (%)	25 (28.0 %)	20 (18.0 %)*	-
	- Patients who recovered after developing complications, N (%)	22 (24.7 %)	14 (15.5 %)	
3.	Adverse cardiovascular events, N (%)	2 (2.2 %)	4 (3.6 %)	0.5800
4.	Nosocomial infection, N (%)	17 (19.1 %)	13 (11.7 %)	0.1500
5.	Acute kidney injury, N (%)	12 (13.5 %)	18 (16.2 %)	0.5900
6.	Seizure, N (%)	10 (11.2 %)	0 (0.0 %)	0.0003
7.	Duration of stay in hospital (days)			
	< 5 days, N (%)	15 (16.9 %)	15 (13.5 %)	0.5000
	5-9 days, N (%)	42 (47.2 %)	57 (51.3 %)	0.5600
	10-15 days, N (%)	22 (24.7 %)	32 (28.8 %)	0.5100
	> 15 days, N (%)	10 (11.2 %)	7 (6.3 %)	0.2100
8.	Death, N (%)	3 (3.4 %)	2 (1.8 %)	0.4800

**4 patients were lost to follow up as they were discharged against medical advice; p value < 0.05 was considered statistically significant;*

by nosocomial infection (n = 13, 11.7 %) and cardiovascular events (n = 4, 3.6 %) in asymptomatic group. Of note, ten patients (11.2 %) in symptomatic group had seizure but none in the asymptomatic group which was significant (p = 0.0003).

Discussion

Presented study targeted on T2DM patients because hypoglycaemia in T2DM is multifactorial and depends on type of therapy (insulin, insulin secretagogues or insulin sensitiser), presence of comorbid conditions and medications. Hypoglycaemia is a complication in hospitalised T2DM patients which causes morbidity and managing in-patient hypoglycaemia still remains a challenge still remains.[10] In presented study, hypoglycaemic events predominantly occurred in patients aged 55 years and older and symptomatic patients were significantly elderly patients. ADA report on impact of hypoglycaemia in elderly states geriatric population are vulnerable to hypoglycaemic events due to decline in renal function, impaired hepatic metabolism of anti-diabetic medications and a decrease in beta-receptor function.[11] Elderly people naturally have long duration of diabetes which also results in absent glucagon response due to diminished paracrine crosstalk between alpha and beta cells.[12] Hence, the American geriatric society recommends target HbA_1c of 8 % in elderly.[13] One of the definitive risk factors which predicts recurrent episodes is past history of hypoglycaemia.[14] Presented study highlights the significant difference between symptomatic and asymptomatic group with regards to prior episode of hypoglycaemia, admission blood glucose and HbA_1c. Criner et al observed significant difference in recurrent hypoglycaemia between symptomatic (13 %) and asymptomatic group (44 %).[14] Marked variation exists in published studies with regards to defining cut off for hypoglycaemia related events. As per ADA 2020, level-1 hypoglycaemia is present when measured blood glucose is < 70 mg/dL, level-2 hypoglycaemia is defined as blood glucose < 54 mg/dL. Severe hypoglycaemia (level-3) is present when severe impairment in mental status or cognitive decline requiring physical assistance for correction of hypoglycaemia.[15] Severe hypoglycaemia occurs with measured blood glucose level < 40mg/dL.[10] Sweating (40 %) and drowsiness (36 %) were the common adrenergic and neuroglycopenic symptom respectively in presented study. Symptomatic group of patients had significantly lower CBG at the time of hypoglycaemia and 34.8 % of symptomatic group had severe hypoglycaemia (CBG < 40 mg/dL). Shriraam et al reported weakness (76.2 %) and dizziness (74 %) as common hypoglycaemic symptom in T2DM patients and 23 % had severe hypoglycaemia in their study.[16] Patients with CBG between 60-69 mg/dL predominantly didn't manifest symptoms (n = 45) whereas only 5 developed symptoms in presented study. Hence clinical practitioners and health care providers should actively seek for patient reported events, low blood glucose values or hypoglycaemic unawareness in every visit. Reported rates of severe hypoglycaemia in published studies varies from 0.7-12/100 person-years.[17]

One of the existing myths in management of diabetes is that higher HbA_1c doesn't cause hypoglycaemia in T2DM.[4] Presented study observed HbA_1c was significantly associated with in-hospital hypoglycaemia in T2DM patients in both symptomatic and asymptomatic group and mean HbA_1c levels was significantly higher in symptomatic group (8.5 %) than asymptomatic group (7.7 %). The diabetes and ageing study by Lipska et al showed hypoglycaemia occurrence across all levels of glycaemic control and 19 % of the people who reported hypoglycaemia had $HbA_1c > 9$ % (n = 187 out of 985 patients with hypoglycaemia).[18] In the Freemantle study, 1 % increase in HbA_1c was reported to have significant increase in frequency of hypoglycaemic episodes.[19] All these findings highlight the significance of occurrence of hypoglycaemia in T2DM patients despite higher HbA_1c.

Hypokalaemia was observed more in asymptomatic group (n = 14, 12.6 %) than symptomatic group (n = 5, 5.6 %) in presented study. Kang et al in their study observed nearly 22 % patients having hypokalaemia during severe hypoglycaemia.[20] This was associated with high blood pressure and tachycardia possibly reflecting sympathetic drive as a response to hypoglycaemia which secondarily induces hypokalaemia by activation of beta adrenoreceptors. Elevated creatinine was noted in 30 % of total patients in presented study. A study done by Carreira et al found hypoglycaemia was 4.2 times higher with acute kidney injury (AKI) and duration of AKI more than 5.5 days is a predictor of hypoglycaemia and mortality.[21] Renal function must be evaluated in all patients with hypoglycaemia, particularly in elderly patients as age related decline in glomerular filtration rate happens and AKI is a precipitating factor for hypoglycaemia.[22] Elderly patients preferably should have a target HbA_1c of 8 % rather than stringent glycaemic control which carries risk of serious hypoglycaemia. Presented study didn't find any significant difference between the two group with regards to length of stay, complications reported including adverse cardiovascular event or mortality possibly due to low event rate observed and smaller sample size and hence causality cannot be claimed from presented findings. In this study, 6 patients had adverse cardiovascular event. ACCORD trial reported hypoglycaemia was three times higher in intensive arm and trail was stopped early in view of serious adverse cardiovascular events and subsequent mortality, though increase in mortality was not directly linked to hypoglycaemia.[23] ADVANCE study also concluded severe hypoglycaemia is associated with higher macrovascular events (Hazard ratio, HR: 2.88), death from cardiovascular cause (HR: 2.68).[24] In presented study, 10 (11 %) of patients who had seizures in the symptomatic group got recovered and discharged from the hospital. Diagnosis of those patients who had seizures include acute on chronic kidney disease (n = 2), bronchial asthma (n = 2), angioedema (n = 1), accelerated hypertension (n = 1), diabetic foot ulcer (n = 2), urinary tract infection (n = 2).

Limitations of this study are that it was not assess the temporal pattern of hypoglycaemia (daytime vs nocturnal events) and recurrent hypoglycaemia in study patients were not studied. For each patient included in this study, the first hypoglycaemic episode only was counted and subsequent number of hypoglycaemic episodes following the first event were not assessed. The clinical characteristics with hospitalised T2DM patients without hypoglycaemia were not compared. Observed event rate of complications is smaller and causality or association with hypoglycaemia cannot be established from this study. Levels of hypoglycaemia as per ADA was not assessed between the groups.

Conclusion

This study showed that symptomatic in-hospital hypoglycaemia in T2DM patients was significantly associated with prior episode of hypoglycaemia and admission blood glucose levels. HbA_1c levels and severe hypoglycaemia were significantly higher in symptomatic group of T2DM patients. Results showed that risk of hypoglycaemia was seen at all levels of glycaemic status in patients with T2DM. Study also highlights that even with sub-optimal HbA_1c levels > 7 %, hypoglycaemia can occur in hospitalised patients with T2DM. Predominant episodes of hypoglycaemia were asymptomatic in hospitalised patients. General practitioners and clinicians should routinely enquire about symptoms of hypoglycaemia in each visit including patient recalled events as well as documented hypoglycaemia without any symptoms.

Ethics

Study approval was obtained from Institutional Research Ethics Committee, SRIHER, India (Decision No: CSP-MED/19/NOV/57/192, dated 29 January 2020).

Acknowledgement

None.

Conflicts of interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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