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# Epidemiology of Hypoglycemia in Type 2 Diabetes Mellitus Patients in Emergency Department: A Retrospective Study in Secondary Care Hospital in India



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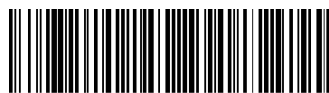
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## ABSTRACT

**Background and Objectives:** Epidemiology of hypoglycemia in westernized societies might not be pertinent to populations in other parts of the world, where a paucity of information about the prevalence of hypoglycemia exists. Epidemiological data in India are limited while hypoglycemia remains a neglected complication of diabetes treatment. The objectives of the study were to analyze length of hospital-stay, demographics such as co-morbid conditions, prescription patterns of anti-diabetic medications and anti-hypertensives associated with hypoglycemia in type 2 diabetes mellitus (T2DM) admitted in emergency department. **Methods:** A retrospective cross-sectional study included T2DM patients admitted in emergency department with hypoglycemia during August 2018 to August 2019 in a secondary care hospital. **Results:** A cohort of 48 subjects with mean age of 71 years, mean blood glucose of 42 mg/dL and length of hospital of 2.7 days were reported. Peak time of hypoglycemic attack was at 8<sup>th</sup> hour in a 24hour distribution. One fourth of total subjects required assistance from another person during severe hypoglycemia. Prevalent symptoms reported were general weakness (25%) and disorientation (12.5%). Patients who were on b-blockers had a low mean blood glucose of 35 mg/dL when compared to non-b blockers (47 mg/dl) [ $P=0.0029$ ]. **Interpretation and Conclusions:** Hypertension (HTN) treatment in T2DM patients have to be modified according to current HTN guidelines thus hypoglycemic unawareness can be avoided. Peak time of hypoglycemic attack at 8<sup>th</sup> hour could be correlated with time just before breakfast and admitted patients had to stay 2.7 days in hospital to recover.

## INTRODUCTION

Hypoglycemia is the prominent complication of diabetes therapy.<sup>[1]</sup> Hypoglycemia requiring hospitalization remains a serious and costly limitation to treatment of type 2 diabetes with antidiabetic medications. Hypoglycemia is one of the most feared complications of diabetes treatment.<sup>[2]</sup> The reported incidence of severe hypoglycemia in IDDM ranges from four to 65 episodes per 100 patient-years.<sup>[3-6]</sup> Hypoglycemia is defined as plasma glucose levels < 70 milligrams per deciliter (mg/dl). However, the symptoms are the driving determinant rather than an absolute glycemic value since the threshold for the onset of symptoms varies among individuals. The symptoms of mild hypoglycemia include sweating, shaking, vision changes, immediate hunger, confusion, and lack of coordination. Severe hypoglycemia occurs when an individual is unable to self-treat due to mental confusion, lethargy, or unconsciousness. Some individuals may experience neuroglycopenia and present with symptoms of crying argumentativeness, inappropriate giddiness, or euphoria.<sup>[7,8]</sup>

Though diabetes mellitus act as one of the main risk factors for cardiovascular diseases and complications, hypoglycemia is the prominent consequence of strict glycemic control. Epidemiological data in India are limited while hypoglycemia remains a neglected complication of diabetes treatment. Purpose of our study was to analyze demographics such as co-morbid conditions, prescription patterns of anti-diabetic medications and anti-hypertensives associated with hypoglycemia in Type 2 diabetes mellitus (T2DM) admitted in emergency department. Hypoglycemia is one among the driving causes for Emergency Department (ED) admissions. The incidence of hypoglycemia in Indian population was 16.51 per 1000 ED visits.<sup>[9]</sup> The incidence of severe hypoglycemia in patients with Type 2 diabetes mellitus (T2DM) varied from 0.0004 to 0.96 episodes per patient per year.<sup>[10,11]</sup> Recurrent hypoglycemia has found to decrease the quality of life diabetes patients. Nevertheless, hypoglycemic agents used in diabetes mellitus are the most prevalent cause for occurring hypoglycemia.<sup>[12]</sup>

## MATERIALS AND METHODS

### *Subjects*

The retrospective cross-sectional study was conducted in the Emergency Department of secondary care hospital in Kerala, India with chief complaint of hypoglycemia in Type 2 diabetics mellites patients. We included the patients with known history of T2DM characteristically presented with Whipple triad: documentation of low blood glucose [capillary blood glucose (CBG) level of  $\leq 70$  mg/dl] in the ED visits, presence of hypoglycemic symptoms, and reversal of these symptoms when blood glucose level was restored. Study period was one year during the period of August 2018 to August 2019.

### *Clinical characteristics*

Hypoglycemia attack was defined as patient's random blood capillary glucose level  $\leq 70$  mg/dl at the time of ED visits and severe hypoglycemia was considered as patients with transient dysfunction of central nervous system who were unable to treat themselves (requiring help from another person). The blood glucose levels were recorded with the help of handheld glucometer using finger pricked capillary blood glucose level in ED triage. Common symptoms experienced included in the study were seizure, sweating, disorientation, giddiness, fatigue, general weakness, anxiety.

### *Data collection*

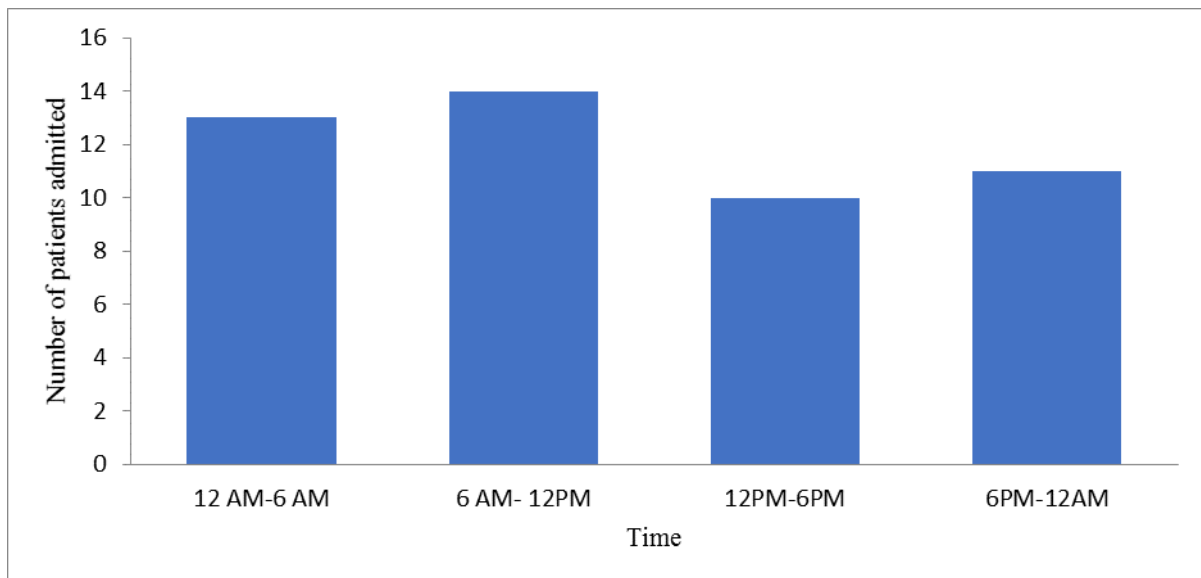
Patient hospital identification number was noted from the ED register along with date of visit, gender and age of the patient. The patient clinical data were fetched from medical records using patient ID number and the data were entered into Microsoft Excel spreadsheet 2019. The entered data was verified and the completed data were analyzed.

### *Statistical analysis*

The summary data are presented either as the mean and standard deviation (SD) or as the number of patients. Multiple logistic regression was done to assess the prediction of patient characteristics on hypoglycemic symptoms. Two-sided  $P$  values  $< 0.05$  were considered as statistically significant. Data analysis was performed using Statistical software SPSS (IBM) version 23 and Microsoft Excel 2019.

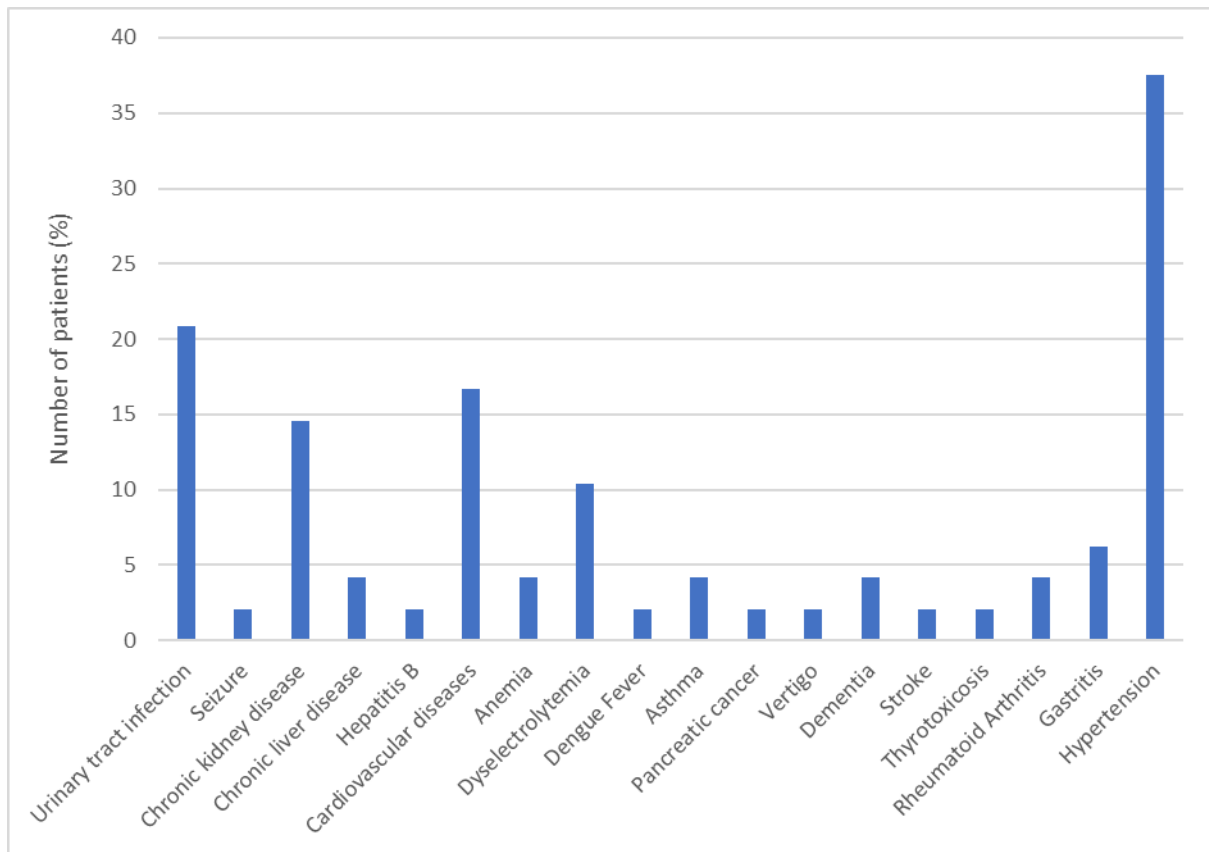
## RESULTS

During our study period, we analyzed a cohort of 48 patients with Type 2 DM admitted with hypoglycemia in the ED. The mean age of the population was found to be  $71 \pm 10.9$ , the youngest being 46 years old and the oldest 90 years of age. Gender distribution was even with 23(48%) female and 25 (52 %) male patients were visited with hypoglycemia attack. The mean random blood sugar at the time of ED visit was  $42 \pm 14.42$  mg/dl. The distribution of ED visits over 24-hour duration reported a peak at 8<sup>th</sup> hour and the time of admission of the patients with hypoglycemia is depicted in **Figure 1**. Most of the patients were having hypertension (37.5%) and the other co-morbidities presented with the diabetes patients are shown in **Figure 2**. T2DM patients admitted with hypoglycemia also showed up with urinary tract infections (20.83%), cardiovascular events (16.66%), chronic kidney diseases (14.58%) and dyselectrolytemia (10.41%) as the major co-morbidities. Mean duration of hospital stay of T2DM patients admitted with hypoglycemia in ED was  $2.7 \pm 2.176$  days.



**Figure No. 1: Time and number of patients admitted with hypoglycemia in the emergency department**

Majority of patients reported during 6 AM-12 PM and least reported time was 12 PM-6 PM. Hypoglycemic attack was more in during night in type 2 diabetes mellitus patients in emergency department.



**Figure No. 2: Co-morbidities of patients along with Type 2 Diabetes Mellitus admitted with hypoglycemia**

Co-morbidities mostly include hypertension, urinary tract infection and cardiovascular disease. Percentage of patients who had other co-morbidities other than type 2 diabetes mellitus are plotted.

Patients admitted with symptom of unconsciousness had a mean blood glucose level of 26 mg/dL and it is categorized under severe hypoglycemic symptoms [Table I]. Three patients were admitted with seizure (6.25%) with mean blood glucose 27.66 mg/dl, other serious hypoglycemic symptoms (47.92%) experienced by patients were reduced response, disorientation, lethargy/Fatigue and inappropriate giddiness. Among them, 12 (25%) required others help during the episode which was reported from bye-standers' dialect. Mild-moderate symptoms of hypoglycemia were evinced by 52.08 % of admitted cohort and the symptoms include sweating, general weakness, confusions, anxiety and immediate hunger with changes in vision.

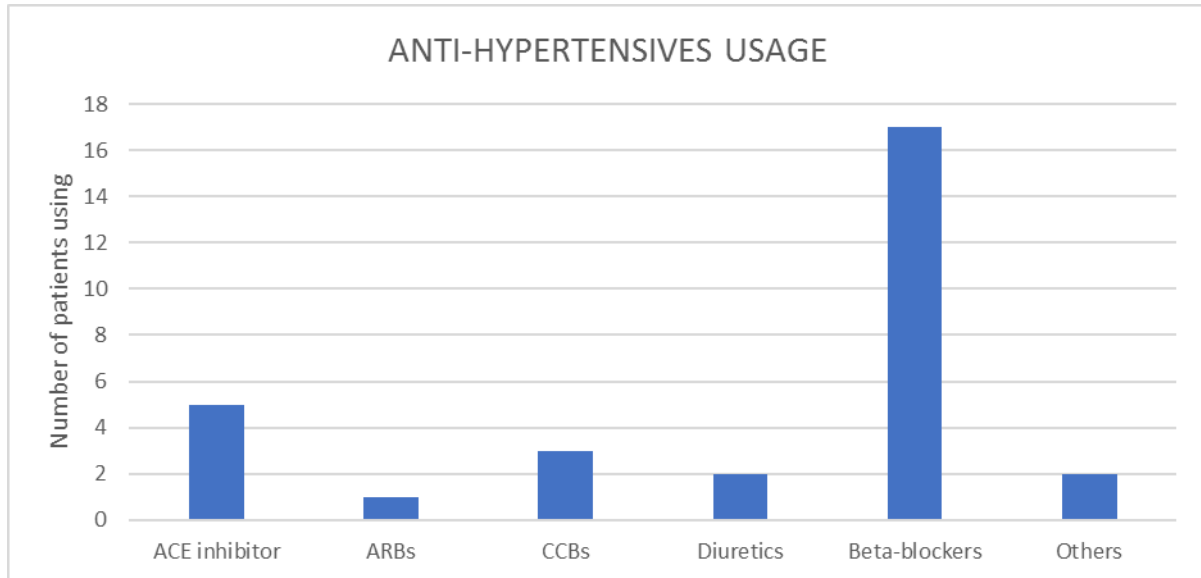
**Table No. I: Hypoglycemic symptoms and blood glucose level**

Symptoms reported	Number (%) of patients admitted	Mean blood glucose (mg/dL)	Range of blood glucose level(mg/dL)
<b>Mild-moderate hypoglycemic symptoms</b>			
Sweating	2 (4.16)	42	27-57
General weakness	12 (25%)	46.08	31-77
Shivering	2 (4.16%)	39.5	38-41
Confusions	3 (6.25%)	75	66-89
Anxiety	3 (6.25%)	53.66	44-63
Immediate hunger with vision changes	3 (6.25%)	40.66	39-45
<b>Severe hypoglycemic symptoms</b>			
Reduced response	2 (4.16%)	38.5	23-54
Disorientation	6 (12.5%)	42	29-51
Lethargy/ Fatigue	4 (8.33%)	44.75	40-51
Giddiness	6 (12.5%)	37.33	20-53
Unconsciousness	2 (4.16%)	26	19-33
Seizure	3 (6.25%)	27.66	21-40

In Table 1, hypoglycemic symptoms were categorized into mild-moderate and severe symptoms based on symptoms reported by the patients and blood glucose level at time of admission. Severe hypoglycemia was considered as patients with transient dysfunction of central nervous system who were unable to treat themselves (requiring help from another person). A patient with blood glucose level of 89 mg/dL was also included since the patient was a victim was recurrent hypoglycemic attack who was on sulfonylurea.

#### ***Hypoglycemia and beta adrenoreceptor blockers (b- blockers)***

The pattern of antihypertensive drug use in diabetes patients are illustrated in **Figure3**. Out of 18 patients who had hypertension, 8 patients had only hypertension as their sole comorbidity other than diabetes mellitus. The use of antihypertensives in 5 patients among those eight were not in accordance with the JNC 8 guidelines and surprisingly these five people reported with hypoglycemic unawareness. In patients admitted with hypoglycemia, those with low blood glucose level (mean of 35.17 mg/dl) had a consumption of beta-blocker as a common factor. We assessed the statistical significance among beta-blocker taking patients (17) and non-beta-blocker consuming patients (31) with their blood glucose. We could find a statistically significant ( $P$  value = 0.0029) discovery after performing student's  $t$ -test.



**Figure No. 3: Antihypertensive usage in Type 2 Diabetes Mellitus patients presented with hypoglycemia**

ACE inhibitor: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blockers, CCBs: Calcium channel blockers, beta-blockers (b-blockers): b- adrenoreceptor blockers. Other antihypertensives was Isosorbide dinitrate (ISDN).

#### *Hypoglycemics prescription pattern*

Patients admitted with hypoglycemia included 9 (18.75%) for sulfonylurea alone, 3 (6.25%) for metformin alone and 8 (16.66%) for any insulin alone treatment was reported with mean capillary blood glucose of 51.77 mg/dl 50 mg/dl and 38.37 mg/dl respectively (**Table II**). A patient treated with combination of metformin, insulin, thiazolidinediones and sodium-glucose transporter protein 2 (SGL2) inhibitor resulted in extremely low CBG (20 mg/dl). She was the only patient in our cohort treated with SGL2 inhibitor (Empagliflozin).

**Table No. II: Combination of hypoglycemic agents used and mean blood glucose at emergency admission in patients with Type 2 Diabetes Mellitus**

Combination of hypoglycemic agents	Number (%) of patients reported with hypoglycemia (N=48)	Mean blood glucose level at admission (mg/dL)
Metformin alone	3 (6.25)	50.00
Metformin and Sulfonylurea	7 (14.58)	48.57
Metformin and Insulin	4 (8.33)	25.75
Metformin and Alpha-Glucosidase inhibitor	2 (4.16)	58.50
Metformin and DPP4 inhibitor	2 (4.16)	36.50
Sulfonylurea alone	9 (18.75)	51.77
Sulfonylurea and DPP4 inhibitor	1 (2.08)	45.00
Sulfonylurea and Alpha-Glucosidase inhibitor	1 (2.08)	35.00
Insulin alone	8 (16.66)	38.37
Metformin, Sulfonylurea, Insulin and Thiazolidinediones	1 (2.08)	29.00
Metformin, Sulfonylurea and Insulin	3 (6.25)	31.66
Metformin, Insulin and DPP4 inhibitor	1 (2.08)	54.00
Metformin, Insulin, Thiazolidinediones and SGL2 inhibitor	1 (2.08)	20.00
Metformin, DPP4 inhibitor and Alpha-Glucosidase inhibitor	2 (4.16)	57.50
Metformin, Sulfonylurea and DPP4 inhibitor	3 (6.25)	44.33

DPP4 inhibitor -Dipeptidyl peptidase-4 inhibitor, SGL2 inhibitor- Sodium glucose cotransporter 2 protein inhibitor.

### ***Subgroups of patients***

Hypoglycemic symptoms experienced by the patients were categorized into patients with mild and severe symptoms [Table 1]. Number of patients evaluated with mild-moderate



symptoms were 25 (52.08%) and patients admitted with severe hypoglycemic symptoms were 23 (47.91%)[ $P=0.0516$ ]. Mean CBG of mild and severe hypoglycemic symptoms were  $46.20 \pm 16.0961$  and  $38.217 \pm 11.2773$  respectively.

Multiple logistic regression analysis was used to determine patient characteristics including drug use independently associated with hypoglycemic symptoms discriminating between patients experienced with mild and severe hypoglycemic symptoms. Severe hypoglycemic symptoms experienced patients were associated with statistically significant ( $P=0.0334$ ) level in the use of sulfonylurea. No significant effects of co-morbidities or age were observed.

## DISCUSSION

In this cross-sectional study, we could find a peak time of reporting hypoglycemia attack at 8<sup>th</sup> hour [Figure 1] in a 24-hour distribution can be correlated with time just before breakfast. Kumar *et al.* an Indian study (2017) showed a bimodal distribution of hypoglycemia episodes of 2 peaks at 8<sup>th</sup> and 21<sup>st</sup> hours attributed just before the meal. However, the patient flow to ED during different hours of the day should also be considered.<sup>[9]</sup> Male and female proportion were more or less even in this study.

Hypertension (37.5%) as predominant co-morbid condition reported in this study. Shriraam *et al.* study showed the prevalence of hypoglycemia in India also had 87.4% of hypertensive co-morbid patients among T2DM.<sup>[13]</sup> Hospital stay associated with hypoglycemia in T2DM was 2.7 days which is consistent with Turchin *et al.* an American study to assess prevalence of hypoglycemia in general ward, the documented increased rate hospital stay due to hypoglycemia was 2.5 days within one year.<sup>[14]</sup>

Every single subject reported one or other symptoms of hypoglycemia. General weakness (25%) and disorientation (12.5%) were prevalent symptoms. Hypoglycemia was severe requiring assistance in 25% of the patients. In an Indian study to assess the hypoglycemic prevalence, one-fifth of subjects required help from another party.<sup>[13]</sup>

Among hypertensive co-morbid T2DM patients, 94.44% had b-blocker as their treatment for hypertension admitted with low mean blood glucose of 35 mg/dl when compared to non-b blockers (47 mg/dl) with statistical significance. This implies a reduced perception of hypoglycemia that is observed in patients who receive b-blockers, confines the use of this

drug category only when it is strictly indicated.<sup>[15]</sup> Gehlaut *et al.* conducted a prospective nonblinded trial in Ohio among 108 T2DM subjects, 54 people had hypoglycemia-14 were on b-blocker of which 11 patients had hypoglycemic unawareness.<sup>[16]</sup>

Initial choice of antihypertensive treatment in T2DM are ACEI/ARB, thiazide like diuretics or CCBs as recommended by Joint National Committee (JNC) 8 guidelines (2014), American Diabetes Association (ADA) in 2018, European Society of Hypertension/European Society of Cardiology (ESH/ESC) in 2013 in contrast, this study had a majority of hypertensive T2DM patients treated with b-blocker which was not in accordance with current recommendations unless under compelling indications such as heart failure (HF) or myocardial infarction (MI).<sup>[17]</sup> It is well-known that beta-blockers might reduce insulin sensitivity and bring on deregulation of T2DM.<sup>[15]</sup>

Combination and monotherapy of hypoglycemic agents presented with hypoglycemia [Table 2] and mean blood glucose at time of admission elucidates a severe hypoglycemia in a patient of triple therapy with insulin resulted in blood glucose of 20 mg/dl which is consistent with prescribing information of empagliflozin by FDA with combination of metformin, pioglitazone and insulin with 28.4% of incidence in severe hypoglycemia.<sup>[18]</sup> Predominant number of hypoglycemia was observed in sulfonylurea alone (18.75%). Insulin alone (16.66%) and sulfonylurea-metformin combination (14.58%) therapies which is congruent with a retrospective interview-based study by Miller *et al.* in 2001, the prevalence of hypoglycemia in sulfonylurea alone (16%), sulfonylurea-metformin combination (18%) and insulin alone (30%).<sup>[1]</sup>

In a cross-sectional India study by Shriraam *et al.* in 2017, 23% of T2DM admitted with hypoglycemia had reported with severe symptoms of hypoglycemia.<sup>[13]</sup> In a prospective multicenter randomized control trial (DCCT) in 1991 in USA, the prevalence of severe symptoms hypoglycemia reported was 33%.<sup>[19]</sup>

In a meta-analysis conducted by Liu *et al.* to determine the comparative efficacy and hypoglycemia associated with OHAs and insulin when compared to placebo, sulfonylurea had odds ratio of 8.86 (95% CI 4.63 to 17.83) and insulin 4.77 (95% CI 1.35 to 18.3) causing severe hypoglycemia whereas, other OHAs have odds ratio of less than one.<sup>[20]</sup>

Admitted patients who were unresponsive/ NPO, managed with IV access of quick administration of dextrose (100 ml vial of Dextrose 25%, 500 ml bottle of Dextrose 5%, 500 ml bottle of DNS) as required by the patient until normalization of blood glucose.

### ***Limitations***

Study was retrospective cross-sectional design, which precludes the calculation of incidence of hypoglycemia thereby hamper direct comparison of study result with DCCT or UKPDS. [21,22]

ADA and Endocrine society workgroups agree that a single threshold value of blood glucose concentrations cannot be set for defining hypoglycemic symptoms in T2DM as the threshold values may shift to lower side in pre-existing hypoglycemics and shift to higher plasma glucose concentrations in poorly controlled T2DM patients. Cut-off value is assigned to draw attention of patients, caregivers to potential harm associated with hypoglycemia.<sup>[21]</sup>

### ***Strength of the study***

One among the first Indian study that highlights the effect of b-blocker in hypoglycemia unawareness and emphasize the frequency of severe hypoglycemic symptoms. Study accentuates the prevalence of hypoglycemics combinations ensued hypoglycemia in T2DM patients admitted in ED along with duration of hospital stay.

### **CONCLUSIONS**

In this study, we conclude that the use of b-blockers in T2DM has to be more discerning to avoid hypoglycemic unawareness. Length of hospital stays associated with hypoglycemia in T2DM patients is 2.7 days. Peak incidence of hypoglycemia attacks at 8<sup>th</sup> hour can be correlated with time just before breakfast. This problem requires to be addressed by physician from in a viewpoint of patient education and modifying medications. Patient education could make them acknowledge the time action profiles of their diabetes medications and realize that excessive treatment can be harmful.

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None


## Conflicts of Interests

Authors declare no conflicts of interests for this article.

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