A Study On Assessing The Hypoglycemic Episodes In Type 2 Diabetes Mellitus Subjects

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Abstract

BACKGROUND: Prevalence of hypoglycemia in Type 2 diabetes is generally under-reported. Making therapeutic adjustments to avoid hypoglycemia is a serious concern for which Continuous Glucose Monitoring System (CGMS) helps in identifying high and low blood glucose values. The study was conducted with the objectives to assess the occurrence of hypoglycemic episodes, and to find the correlation between HbA1c and hypoglycemia among type 2 DM subjects.

METHODOLOGY: A cross-sectional study was conducted among 50 subjects over 18 months. Considering the inclusion and exclusion criteria, patients were subjected to CGMS using FREESTYLE LIBRE PRO. The data was collected for 24 hours for a period of 14 days and was expressed in means and proportions. Correlation was elicited using Pearson's Correlation test.

RESULTS: Mean age of the study subjects was 54.78+9.49 years. Majority (70%) were males and 72% were on oral hypoglycemic agents. 16% gave history of previous hypoglycemia. 32% had at least 1 episode of hypoglycemia (Mean of 1.1 episodes/patient/14 days of CGMS) and more than 50% of those had severe hypoglycemia. Levels of HbA1c with the occurrence of hypoglycemic episodes showed a negative correlation ($P<0.05$).

CONCLUSION: More than 1/3rd patients had at least one episode of hypoglycemia and 50% of those had severe hypoglycemia. >1 episode per patient with hypoglycemia in 14 days of CGMS and proportions with hypoglycemia calls for urgent action. The occurrence of hypoglycemia with decreasing levels of HbA1c indicates strict therapeutic control. Previous history of hypoglycemia is an indicator for further follow up.

Keywords: Hypoglycemia, CGMS, T2DM

Introduction

Diabetes, a chronic progressive disease is an important public health problem which is characterized by elevated levels of blood glucose. There is a high predisposition to type 2 diabetes mellitus (T2DM), among Asian Indians, which develops at a younger age and lower BMI than in western countries.[1,2,3] In young and adult patients, the main treatment goal has been strict glycemic control aimed at bringing the hemoglobin Alc (HbA1c) level to within normal values (i.e., ≤6.0%). In older patients with T2DM, a history of severe hypoglycemia is associated with higher mortality risk, more severe microvascular complications and greater risk of dementia. Thus, patients with suspected or documented episodes of hypoglycemia,

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especially those who are frail or disabled, need more liberal glucose-control goals, careful education about hypoglycemia and dose follow-up by the health care provider.[11]

Hypoglycemia has been defined by American Diabetes Association (ADA) as severe hypoglycemia, documented symptomatic hypoglycemia, asymptomatic hypoglycemia, probable symptomatic hypoglycemia, relative hypoglycemia as follows:

1. Severe Hypoglycemia: An episode requiring the assistance of another person to raise the plasma glucose concentration resulting in resolution of symptoms, with or without a measured low plasma glucose concentration.

2. Documented Symptomatic Hypoglycemia: Symptoms consistent with hypoglycemia with a measured plasma glucose concentration <70mg/dL.

3. Asymptomatic Hypoglycemia: A measured plasma glucose concentration <70mg/dL in the absence of symptoms.

4. Probable Symptomatic Hypoglycemia: Typical symptoms of hypoglycemia without a measured plasma glucose concentration.

5. Relative Hypoglycemia: Typical symptoms of hypoglycemia with a measured plasma glucose concentration >70mg/dL but approaching that level.(Such episodes occur in people with poorly controlled diabetes).[14]

Hypoglycemia has been a common side effect of diabetes therapy, leading to a wide range of neurogenic and neuroglycopenic symptoms, such as, palpitations, sweating, headache, feeling hungry, shivering, restlessness, anxiety, confusion, coma, in turn, leading to death. In the absence of these warning symptoms, which normally occur at lower plasma glucose <60 mg/dl, the brain becomes neuroglycopenic and promotes secretion of counter-regulatory hormones, primarily, adrenaline and norepinephrine along with glucagon, the "rapid" responses, which have corresponding cardiovascular effects.[13] Hypoglycemia impairs defenses because of autonomic failure (Hypoglycemia Associated Autonomic Failure-HAAF) and is also causally linked to neuro-cognitive deterioration.

Almost 50% of all episodes of severe hypoglycemia are nocturnal and expected to be under-reported.[18,20] Episodes of nocturnal hypoglycemia can cause convulsions and coma and have been implicated as a precipitating factor in cardiac arrhythmias resulting in sudden death- "dead-in-bed syndrome".[20]

In this background, it can be noted that making adjustments in the therapy of diabetes is a serious concern to avoid hypoglycemia for which Continuous glucose monitoring system (CGMS) aids in gauging the effectiveness of therapy that can dramatically improve patients' glycemic control and reduce the risk of long-term complications even in terms of hypoglycemia.[21,22,23]

Methodology

A cross-sectional study was conducted at Department of General Medicine, Kempegowda Institute of Medical Sciences Hospital, Bangalore, Karnataka, over a period of 18 months. 50 patients aged >18 years diagnosed with Type 2 DM for duration of >5 years and on treatment for the same were considered for the study.

Inclusion Criteria

Patients aged >18 years diagnosed with Type 2 DM with a duration of >5 years and on treatment with either sulfonylureas or Insulin or both who were willing to participate were considered for the study.

Exclusion Criteria

1. Subjects diagnosed with type 1 diabetes mellitus

2. Subjects who have diabetic nephropathy

3. Subjects having evidence of congestive cardiac failure (Ejection fraction <40%)

4. Subjects with Acute febrile illness, critically ill patients or hospitalized patients, evidence of impaired renal function, having any hepatic disease.

5. Subjects who are fasting.

After approval by the Institutional Ethics Committee, a written informed consent was taken prior to the recruitment of patients in the study & relevant details regarding the purpose, investigations to be carried out, study procedure & potential hazards were explained to the patients in their own language.

Methods of Data Collection

A pre-tested questionnaire consisting of baseline data which included the socio-demographic data, details on medical history including conventional risk factors, clinical examinations and relevant investigations was used to collect the data. After obtaining the written informed consent, detailed clinical history was taken from patients as per the proforma.

All the patients were examined and subjected to relevant investigations that included the following:

a) CBC, ESR, peripheral smear

b) FBS, PPBS, HbA1c

c) Renal function tests

d) Serum electrolytes

e) Liver function tests

f) Fasting lipid profile

g) Urine routine

h) ECG

i) Fundoscopy

j) Echocardiography

All the patients were subjected to Continuous glucose monitoring using FREESTYLE LIBRO PRO approved by FDA. The continuous glucose monitoring uses the interstitial fluid sample and records the glucose levels every 15 mins and the data was collected for a 24 hours period and a series of such data was collected for 14 days.

Statistical Analysis:

The HbA1c levels with the occurrence of hypoglycemia and number of episodes of hypoglycemia were correlated using Pearson's Correlation test. The analysis was done SPSS version 16.0. A P value of <0.05 was taken as statistically significant.

Results

Table 1: Distribution of study subjects based on presenting complaints

Presenting Complaints	Number (n)	Percentage (%)
Routine Check up	30	60.0
Easy Fatiguability	13	26.0
Increased frequency of Urine	04	08.0
Excessive Sweating	03	06.0
Total	50	100.0

The above table shows that majority i.e., 30, 60.0% of them had come for routine check-up.

Table 2: Distribution of study subjects based on presence of previous history of hypoglycemia

Hypoglycemia	Number (n)	Percentage (%)
Present	08	16.0
Absent	42	84.0
Total	50	100.0

Among the diabetic patients, only 8, 16.0% had hypoglycemia and majority i.e., 42, 84.0% did not have hypoglycemia.

Table 3: Mean blood glucose levels based on CGMS on Day 0, 1 and 14

Days of measurement	Mean blood glucose values (Mean ± SD)
Day 0	221.14±81.75
Day 1	208.50±68.01
Day 14	184.02±58.53

The mean blood glucose values on days 0, 1 and 14 of CGMS measurements were 221.14±81.75 mg/dl, 208.50±68.01 mg/dl and 184.02±58.53 respectively. The blood glucose values on CGMS measurements ranged from 103 mg/dl to 459 mg/dl on day 0, 110 mg/dl to 456 mg/dl on day 1 and 84 mg/dl to 346 mg/dl on day 14. The average blood glucose values on of CGMS recorded over 0, 24 hrs and 14 days was 204.53±60.95 mg/dl and it ranged from a minimum 84 mg/dl to 459 mg/dl.

Table 4: Proportion of study subjects based with Hypoglycemia on Day 0, Day 1 at 24 hrs, Day 14

Day	Hypoglycemia	Number (%)
Day 0	Present	02 (4.0)
	Absent	48 (96.0)
Day 1 at 24 hrs	Present	08 (16.0)
	Absent	42 (84.0)
Day 14	Present	20 (40.0)
	Absent	30 (60.0)

Among the 50 subjects, 2 i.e., 4.% had hypoglycemic episodes on day 0 based on CGMS recordings, while 48 i.e., 96.0% did not. The mean number of episodes of hypoglycemia was 1 ± 0.00. On day 1, 8 i.e., 16.0% had hypoglycemic episodes. The median number of episodes on day 1 was 1 and the number of episodes varied from 1 - 7. On day 14, 20 i.e., 40.0% had hypoglycemia. The median number of episodes was 2 and the number of episodes varied from 1 - 7.

Table 5: Association of variables associated with diabetes with occurrence of hypoglycemia

Variables associated with diabetes	Hypoglycemia		χ^2 – Value (*P*-Value)
	Present (%)	Absent (%)	
1. H/o previous episodes of hypoglycemia			
Yes	06 (75.0)	02 (25.0)	**8.09**
No	10 (23.8)	32 (76.2)	**(0.004)***

2. Co-morbidities along with DM			
Present	05 (25.0)	15 (75.0)	**0.75**
Absent	11 (36.7)	19 (63.3)	**(0.39)**
3. Type of treatment for DM			
OHA	12 (33.3)	24 (66.7)	**0.39**
OHA + Insulin	03 (33.3)	06 (66.7)	**(0.83)**
Insulin	01 (20.0)	04 40.0)	
4. Complications – Retinopathy			
Present	03 (23.1)	10 (76.9)	**0.64**
Absent	13 (35.1)	24 (64.9)	**(0.42)**

*Indicates a significant statistical association between the variables on diabetes with occurrence of hypoglycemia at P<0.05.

The proportion of those with hypoglycemia presented with history of previous episodes of hypoglycemia (75.0%) compared to those with no previous history of hypoglycemia (23.8%). The proportion was also higher among those who did not have associated co-morbidities (36.7%) compared to those who had associated co-morbidities (25.0%). The hypoglycemics proportion also seemed to be equal among those who were on OHA's (33.3%) and OHA with insulin (33.3%) compared to those who were on insulin alone (20.0%). Majority of those with hypoglycemia did not have retinopathy findings (35.1%) and only 23.1% had retinopathy findings. However, only previous history of hypoglycemia was significantly associated with the occurrence of hypoglycemia (*P*<0.05) and none others were statistically associated (*P*>0.05).

Table 6: Comparison of FBS, PPBS, HbA1c values and duration of diabetes with occurrence of hypoglycemia and severe hypoglycemia

Particulars	Hypoglycemia		t – value [95% C.I]	*P*-value
	Present (Mean ± SD)	**Absent (Mean ± SD)**		
FBS in mg/dl	156.69±39.19	176.09±58.14	1.21 [-12.87 to 51.68]	0.23
PPBS in mg/dl	211.75±51.80	238.53±70.92	1.35 [-13.17 to 66.73]	0.18
HbA1c in %	8.03±1.17	9.06±2.16	1.78 [-0.13 to 2.19]	0.08
Duration of Diabetes in years	8.13±1.85	8.85±3.33	0.82 [-1.07 to 2.52]	0.42

Particulars	Severe Hypoglycemia		t – value [95% C.I]	P-value
	Present (Mean ± SD)	**Absent (Mean ± SD)**		
FBS in mg/dl	160.75+31.22	171.62+56.54	0.53 [-30.69 to 52.44]	0.18
PPBS in mg/dl	206.38+40.48	234.45+69.36	1.10 [-23.07 to 79.22]	0.19
HbA1c in %	7.96+1.15	8.88+2.04	1.22 [-0.59 to 2.42]	0.23
Duration of Diabetes in years	8.13+1.87	8.71+3.11	0.52 [-1.71 to 2.88]	0.61

The mean values of FBS, PPBS, HbA1c and mean duration of diabetes were not statistically significant in the hypoglycemic group ($P > 0.05$) and the severe hypoglycemic group compared to non hypoglycemic group ($P > 0.05$).

Discussion

Considering India as one of the epicenters of the global diabetes pandemic, appropriate interventions are necessary in order to reduce disease burden.[3,8] Hypoglycemic episodes, especially when severe or recurrent may result in significant psychosocial dysfunction and low quality of life. Nearly 50% severe hypoglycemic episodes occur at night during sleep and data is under-reported.[20] Thus the study was conducted to elicit the occurrence of hypoglycemic episodes along with its correlation to HbA1c.

The mean age of the study subjects was 54.78 ± 9.49 years in the current study which is comparable to a study finding by Dissanayake HA *et al*., wherein the mean age was 55.0± 12.5 years.[39,40,41] According to a study done by Pai SA and George P and Dissanayake

HA *et al*., majority were males which are similar to the current study (70%).[40,42]

Easy fatiguability, polyuria, excessive sweating were the common symptoms among our patients however Borah M and Goswami RK reported polyuria, polyphagia, polydipsia, nocturia as presenting symptoms.[43] The excessive sweating in our study indicates early adrenergic symptoms implicating the established occurrence of hypoglycaemia.[39]

In the current study, only 16% diabetics had previous history of hypoglycemia. Namba M *et al*., in their study noted 37.2% of diabetics had hypoglycemia.[44]

Seth P *et al*., reported that majority i.e., 64% were only on insulin therapy followed by 2%, on combination - insulin and OHAs therapy and least i.e., 16% were on OHAs. However, the proportions

of those who were on OHAs and insulin were reverse in this which may due to the difference in the status of glycemic control over the years.[45]

The CGM tests carried out by Ishikawa T *et al*., for 3.7 ± 1.2 days on an average, recorded mean blood glucose levels to be 164.7 ± 36.3 mg/dl and it ranged from 76.7 ± 25.9 mg/dl to 297.2 ± 67.5 mg/dl, however the average blood glucose values on mean number of days of 0, 1 and 14 of CGMS measurements was 204.53 ± 60.95 mg/dl and it ranged from a minimum 84 mg/dl to 459 mg/dl indicating the better glycemic control in their settings.[50]

Among the 50 study subjects, 32% had at least one hypoglycemic episode during the CGMS recordings. In another study that investigated hypoglycemia in type 2 diabetes patients for 5 days using CGM, 49.1% of participants had at least one hypoglycemic episode.[51]

Our study subjects with at least 1 episode of hypoglycemia experienced 1.1 episodes/patient/ 14 days of CGMS and similarly in a study by Gehlaut RR *et al*., of the patients, who experienced at least 1 hypoglycemic episode, the mean episode was 1.74 episodes/patient/5 days of CGMS.[51] We recorded 50% of hypoglycemics to have severe episodes of hypoglycemia.[52]

The proportion of hypoglycemics, presented with previous episodes of hypoglycemia (75%) were higher compared to those with no previous history (23.8%) and is in concordance with the findings by Samman A *et al*.[51] The proportion of hypoglycemics was also noted to be higher among those who did not have associated co-morbidities (36.7%). The hypoglycemics proportion also seemed to be equal among those who were on OHA's (33.3%) and OHA with insulin (33.3%) compared to those who were on insulin alone (20%). Oral agents have been reported with lower rates of hypoglycemia compared to insulin.[58] Seth P *et al*., has reported similarly that the proportion of those with hypoglycemia were higher with insulin.[45] Bordier L *et al*., found that hypoglycemia was associated with retinopathy, however, it was not associated in this study and it may be because of the fact that the duration of diabetes in their patients are higher compared to ours and hence the proportion of occurrence of complications might be high.

The mean values of FBS were less among those with hypoglycemia and severe hypoglycemia group compared to those without, in the current study which are similar to the findings on FBS by Dissanayake *et al*.[40] The mean values of HbA1c showed a similar pattern but were not significantly different ($P > 0.05$) indicating that that aggressive glycemic management can be associated with increased risk for hypoglycaemia.[39] Similarly in a study by Kalra S *et al*., the hypoglycemia scores and HbA1c values had a significant weak negative correlation.[28] Dissanayake *et al*., also reported patients with hypoglycemic episodes to have a significantly higher duration of diabetes compared to those without, however in the current study, the mean duration of diabetes were not significantly different in hypoglycemia and severe hypoglycemia group as there is difference in distribution duration of diabetes.[40]

HbA1c levels and mean number of episodes of hypoglycemia showed significant negative correlation and similarly in various studies, frequency of hypoglycemia and glycemic control were consistently reported i.e., it was observed more frequently in intensive therapy arms of large studies like UKPDS, ACCORD, ADVANCE, and VADT.[27,28,37,60,61] An inverse relationship was also observed between all confirmed hypoglycemia episodes and HbA1c at endpoint.[28,62]

Conclusion

1. Among the 50 study subjects, 32% experienced at least one episode of hypoglycemia and 50% of those with hypoglycemia had severe hypoglycemia. Such hypoglycemic episodes are often neglected and so needs careful attention as it can be life threatening. Hence modifying a treatment plan that is acceptable to the patient becomes important.

2. The occurrence of hypoglycemia and mean number of episodes of hypoglycemia increases with decreasing levels of HbA1c.

3. Among the different variables, previous history of hypoglycemia was significantly associated with the occurrence of hypoglycemia and hence warns against further hypoglycemic episodes which have to be taken care during follow up.

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