



A STUDY OF HYPOGLYCEMIA IN TYPE 2 DIABETES MELLITUS PATIENTS USING CONTINUOUS GLUCOSE MONITORING SYSTEM

Dr Prabhakar K SDUAHER

Dr M Sasi Sekhar* SDUAHER. *Corresponding Author

Dr Anitha. A SDUAHER.

ABSTRACT

The study was conducted with the objectives to assess the proportion of occurrence of hypoglycaemia, its episodes and to find the correlation between HbA1c and hypoglycemia among the subjects with type 2 diabetes mellitus subjects. **Methodology:** This is a cross-sectional study conducted among a total of 50 subjects for a period of 18 months. Considering the inclusion and exclusion criteria, with basic data collection, all the study subjects were subjected to Continuous Glucose Monitoring using FREESTYLE LIBRE PRO approved by FDA. The data was collected for a whole 24 hour period and a series of such data was collected for 14 days and was expressed in means and proportions. Correlation was elicited using Pearson's Correlation test. The analysis was done by SPSS version 16.0. A P value of <0.05 was taken as statistically significant. **Results:** Mean age of the study subjects was 54.78 + 9.49 years. Majority i.e., Seventy percent (70.0%) were males and Seventy Two percent (72.0%) were on oral hypoglycaemic agents. Sixteen percent (16.0%) gave history of previous hypoglycaemia. Thirty Two (32.0%) had atleast 1 episode of hypoglycaemia (Mean of 1.1 episodes/patient/14 days of CGMS) and more than Fifty (50.0%) of those had severe hypoglycaemia. Levels of HbA1c with the occurrence of hypoglycaemia and mean number of episodes of hypoglycemia showed a negative correlation however it was significant with mean number of episodes ($P < 0.05$). **Conclusion:** The occurrence of hypoglycaemia with decreasing levels of HbA1c indicates the strict therapeutic management. Previous history of hypoglycaemia is an indicator for further hypoglycaemia occurrence and has to be taken into account during the follow up of such cases.

KEYWORDS : Hypoglycaemia, Continuous Glucose Monitoring, Type 2 Diabetes Mellitus, Freestyle Libre Pro

INTRODUCTION

In India, over 74 million cases of diabetes have been living.¹ Every adult over the age of 40 is at risk for diabetes, but no awareness of the disease exists in the country. Over one million Indians die each year due to diabetes.² India has been considered as one of the epicentres of the global diabetes mellitus pandemic.³ To reduce such a disease burden that diabetes creates in India, appropriate interventions by targeting to facilitate screening and early detection programmes, diabetes prevention, self-management counselling, and therapeutic management of diabetes in accordance with the appropriate local guidelines are required.⁴

Though, overall objective of management of type 2 diabetes is to achieve and maintain blood glucose control and reduce the risk of long-term complications and even many studies though show that modern management with intensive glycaemic control can limit, delay or even prevent the chronic complications of diabetes, such intensive diabetes treatment could be associated with an increased risk of hypoglycaemia.⁵

Hypoglycemia has been a common side effect of diabetes therapy, resulting in a lack of adequate cerebral glucose supply, leading to a range of neurogenic and neuroglycopenic symptoms, which in turn can lead to death, if not treated on time.⁵ The incidence of hypoglycemia is comparatively lower in T2DM than T1DM.⁶

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) helps to identify the patterns of both high and low blood glucose values; thus aids in gauging the effectiveness of therapy changes on the patient's blood glucose trends that can dramatically improve patients' glycaemic control and reduce the risk of long-term complications even in terms of hypoglycemia.⁷⁻⁹

In addition to all these, paucity exists in the literatures depicting the prevalence of hypoglycemia in this part of south

India.¹⁰ Hence the study was conducted using a continuous glucose monitoring system with the objectives: -

- To assess the proportion of occurrence of hypoglycaemia and its episodes in type 2 diabetes mellitus subject.
- To find the correlation between HbA1c and hypoglycaemia in type 2 diabetes mellitus subjects.

METHODOLOGY

Study setting: The study was conducted at Department of General Medicine, SRI DEVARAJ MEDICAL COLLEGE and RL JALAPPA Hospital, Kolar

Study design: Cross-sectional study

Study duration: 3 months

Sample size: 50 cases

Sampling: Purposive

Sample size calculation:

Considering the 96.0% prevalence of hypoglycemia among as per literature in India, with 95% confidence interval and absolute error (L) of 36, the total sample size of 40.96 was calculated. The formula used was $n = z^2(pq/L^2)$, where, $z = 1.96$ at 95% confidence interval, $p =$ estimated prevalence (96.0%), $q = 100 - p$ (4.0%) and $L =$ permissible error (absolute error of 6%), the total sample size of 50 was considered for the study. The sample size of 41 was obtained. Considering the non-response rate of 10.0%, $41 + 4 \approx 45$ was the minimum sample size. For the convenience of analysis, minimum of 50 were selected.¹⁰

Method of data collection

50 Patients, aged > 18 years diagnosed with Type 2 Diabetes Mellitus for a duration of more than 5 years, and on treatment for the same were considered for the study.

Inclusion Criteria: - Patients aged > 18 years diagnosed with Type 2 Diabetes Mellitus for a duration of > 5 years and on treatment with either Sulfonylureas or Insulin or both and who

were willing to participate were considered for the study.

Exclusion Criteria:- Subjects diagnosed with type 1 Diabetes Mellitus, Diabetic nephropathy, Subjects having evidence of Congestive Cardiac Failure (Ejection fraction <40%), Subjects with Acute febrile illness, critically ill patients or hospitalized patients, evidence of impaired renal function or having any hepatic disease, Subjects who are fasting.

The diagnosis of type 2 diabetes mellitus was established based on clinical history, treatment history, impaired Fasting and Post Prandial glucose tests, Glycosylated Haemoglobin and Urine routine examinations. Written informed consent was taken prior to the recruitment of patients into the study & relevant details regarding the purpose, investigations to be carried out, study procedure & potential hazards of the study was explained to the patients in their own language. A semi-structured and 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. All the study subjects 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 whole 24 hour period and a series of such data was collected for 14 days.

Statistical Analysis:

The collected data were entered into an excel sheet. The continuous data were expressed in means and standard deviations. The discrete data were expressed in proportions. The HbA1c levels with the occurrence of hypoglycemia and number of episodes of hypoglycaemia were correlated using Pearson's Correlation test. The analysis was done by SPSS version 19.0.

P value of <0.05 was taken as statistically significant.

RESULTS

In the present study, out of 50 study subjects, majority i.e., 64.0% of the study subjects were between 46-60 yrs. age group followed by 20.0% were in the age group > 60 yrs. The mean age of the study subjects was 54.78 ± 9.49 years with a range from 34 to 76 years.

70 % (35/50) were males and remaining 30.0 % (15/50) were females. 64.0% of the study subjects were employed and remaining 36.0% of them were currently either unemployed (retired) or were housewives. 60.0% (30/50) had Diabetes alone followed by Hypertension as coexisting co morbidity was present in 30%(15/50) of the patients; Ten percent (5/50) had other co morbidities along with Diabetes viz., Hypothyroidism in 40.0%(2/5), Pulmonary Koch's in 20.0%(1/5), asthma in 20.0%(1/5) and seizures disorder in 20.0%(1/5) of the study subjects.

The mean duration of diabetes was 8.6 years \pm 2.9 years and it ranged from a minimum of 5.5 years to 20 years. Most of the study subjects i.e., 72.0% were on oral hypoglycaemic agents (OHA) followed by 18.0% were on both OHA's and insulin and only 10.0% were on insulin. Among the study subjects, majority i.e., 64.0% were on mixed type of diet and 36.0% were vegetarians. Among the 50 study subjects, 18.0%(9/50) were smokers. All the smokers i.e., 18.0% smoked cigarettes. Among all the 50 study subjects, 28.0%(14/50) consumed alcohol, majority i.e., 57.14%(8/14) consumed beer and remaining 42.85%(6/14) consumed whisky.

Majority i.e., 44.0% of them were in normal range of BMI followed by 28.0% were in obesity grade I, 26.0% were in overweight and only 2.0% were in obesity grade II. The mean height of the subjects was 165.46 ± 7.04 cms. The mean weight of the subjects was 65.48 ± 8.53 kgs. The mean BMI (Body Mass Index) was 23.87 ± 2.56 kg/m².

The mean FBS, PPBS and HbA1c values were 169.88 ± 53.19 mg/dl, 229.96 ± 66.08 mg/dl and 8.73 ± 1.95 % respectively. Only 2.0%(1/50) of the subjects had anaemia and 14.0% had dyslipidaemia. 13(26.0%) out of the 50 study subjects had abnormal funduscopy findings. 69.2%(9/13) had Grade 1 and Grade 2 non proliferative diabetic retinopathy and 15.4%(2/13) had hypertensive retinopathy and the rest 15.4% (2/13) had both Hypertensive and diabetic retinopathy findings. Patients with Proliferative retinopathy were not included in this study. 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.

Among the 50 study subjects, 16(32.0%) subjects had at least one episode of hypoglycaemia in the 14 day period. Our study subjects experiences at least 1 episode of hypoglycaemia i.e, 1.1 episodes/patient/ 14 days of CGMS.

34(68.0%) of the subjects did not have any hypoglycaemic episodes during the study.

Among the 50 study subjects, 2(4.0%) had hypoglycaemia episodes on day 0 based on CGMS recordings. The mean number of episodes of hypoglycaemia on day 0 among those who presented with hypoglycaemia was 1 ± 0.00 .

96% (48/50) of the study subjects did not have any hypoglycemic episodes on day 0

Among the 50 study subjects, 8 subjects (16.0%) had hypoglycaemia episodes on day 1 based on CGMS recordings. The median number of episodes of hypoglycaemia on day 1 among those who presented with hypoglycaemia was 1 and the number of episodes varied from 1 - 7.

42 subjects (84.0%) of the study subjects did not have hypoglycaemic episodes on day 1.

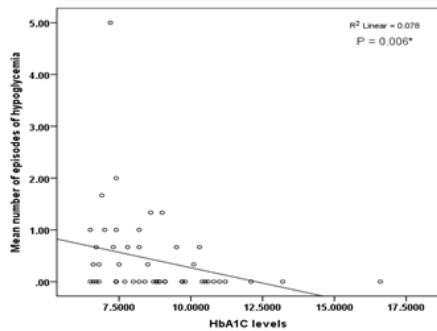
Among the 50 study subjects, 16 i.e., 36.0% had hypoglycaemia episodes at the end of day 14 based on CGMS recordings. The median number of episodes of hypoglycaemia at the end of day 14 among those who presented with hypoglycaemia was 2 and the number of episodes varied from 1 - 7. 34 (60.0%) of the study subjects did not have hypoglycaemic episodes in the whole 14 day study period. Among the 50 study subjects, 16 subjects (32%) had hypoglycaemia in the 14 day period. Out of the 16 subjects who had hypoglycaemia, 8(50.0%) had severe hypoglycaemia i.e, GRBS <40mg/dl based on CGMS recordings. The median number of episodes of hypoglycaemia was 1 on days 0 and day 1 and it was 2 on day 14.

The percentage of study subjects with hypoglycaemia and the proportion of those experiencing hypoglycaemia were more on day 14 (40%) and day 1 (16%) compared to day 0.

Table 1: Comparison of FBS, PPBS, HbA1c values, age and duration of diabetes with occurrence of severe hypoglycaemia

	Hypoglycaemia		P- value
	Present (Mean±SD)	Absent (Mean±SD)	
FBS in mg/dl	160.75+31.22	171.62+56.54	0.18
PPBS in mg/dl	206.38+40.48	234.45+69.36	0.19
HbA1c in %	7.96+1.15	8.88+2.04	0.23
Age	50.63+8.42	55.57+9.58	0.18
Duration of Diabetes in years	8.13+1.87	8.71+3.11	0.61

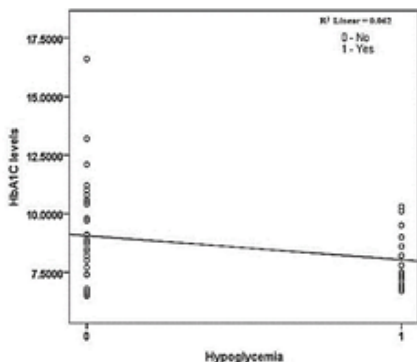
The mean values of FBS were less among those with severe hypoglycaemia (160.75±31.22 mg/dl) compared to those without hypoglycaemia (171.62±56.54 mg/dl) ($t = 0.53, P > 0.05$). The mean values of PPBS were less among those with hypoglycaemia (206.38±40.48 mg/dl) compared to those without hypoglycaemia (234.45±69.36 mg/dl) ($t = 1.10, P > 0.05$). The mean values of HbA1c were less among those with hypoglycaemia (7.96±1.15%) compared to those without hypoglycaemia (8.88±2.04%) ($t = 1.22, P > 0.05$). Similarly the mean age of the subjects with severe hypoglycaemia were lesser (50.63±8.42 yrs) compared to those with no severe hypoglycaemia (55.57±9.58 yrs). However the mean values of FBS, PPBS, HbA1c, age were not significantly different ($P > 0.05$). The mean duration of diabetes were not significantly different in hypoglycaemia group (8.13±1.87 yrs) compared to the group with no hypoglycaemia (8.71±3.11 yrs) ($P > 0.05$).



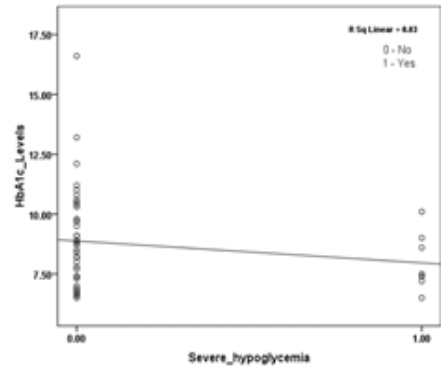
Graph 1: Correlation of HbA1c with mean number of episodes of hypoglycaemia

The above graph indicates the correlation of HbA1c levels with mean number of episodes of hypoglycaemia. HbA1c levels and mean number of episodes of hypoglycaemia showed negative correlation indicating that the number of episodes of hypoglycaemia increased significantly with decrease in the HbA1c levels ($P < 0.05$).

Graph 2:- correlation of HbA1c levels with hypoglycaemia and severe hypoglycaemia



HbA1c levels with occurrence of hypoglycaemia and severe hypoglycaemia showed negative correlation indicating that



the hypoglycaemia and severe hypoglycaemia occurs with decrease in the HbA1c levels, however it was not statistically significant ($P > 0.05$).

DISCUSSION

Shriraam V *et al.*, reported major proportion of the subjects (54.0%) to be in the age group of up to 60 years as compared to the current study findings wherein, 64.0% were between 46-60 yrs age group. The proportions are comparatively higher in the current study due to the difference in the study settings and the different demographic characteristics in the comparative study.¹⁰ 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.¹¹ The age of the study participants ranged between 34 to 76 years and is in concordance with the study finding by Iloh GUP and Collins PI wherein the age of the patients ranged from 32 to 78 years however they found a mean age of 44 ± 10.2 years among type 2 diabetic patients and majority i.e., 59.3% were females and 40.7% were males which were not in line with the current study findings except for the range of age which may be due to the different study settings and different demographic characteristics.¹² But the findings by Pai SA and George P and Dissanayake HA *et al.*, found major chunk to be males which are similar to the current study.^{11,13}

In a study by Borah M and Goswami RK, 25.0% were either retired or unemployed or were housewives. In our study, higher proportions were recorded (36.0%) and is because of different age and gender distributions.¹⁴

The mean duration of diabetes was 8.6 years ± 2.9 years and is similar to the findings by Dissanayake HA *et al.*, wherein the mean duration of diabetes was 10.6 years (± 8.1).¹¹

Seth P *et al.*, reported that majority i.e., 64% were on only insulin therapy followed by 20.0% were on combination of insulin and OHAs therapy and least i.e., 16% were on OHAs. However compared to the Seth P *et al.*, study, the proportions of those who were on OHAs and insulin were reverse which may due to the difference in the chronicity of diabetes and status of glycaemic control over the years.¹⁵

18.0% of our study subjects were smokers and the same proportion had history of alcohol intake in our study. In a study by Krishnan D *et al.* 9.0% were smokers and were alcoholics however the distribution differs because of different study settings.¹⁶

The mean BMI (Body Mass Index) was 23.87 ± 2.56 kg/m² in our study however it was reported to be 29.7 ± 5.7 kg/m² in a study by Cvetanović G *et al.*¹⁷ The mean BMI values were not significantly different among the groups with and without hypoglycaemia and is in line with the findings by Cvetanovic G *et al.* and Ishikawa T *et al.*^{17,18}

The mean FBS and HbA1c values in the current study were 169.88 ± 53.19 mg/dl and 8.73 ± 1.95 % respectively. Dissanayakeet *al.*, found the mean levels of fasting plasma glucose as 7.48 mmol/l (± 2.79) i.e., 137.77 ± 50.27 mg/dl on conversion and mean HbA1c 7.82% (± 1.71) which are slightly lesser compared to current study. Similarly, mean Post Prandial values of diabetic patients in Bamanikar SA *et al.*, study was 168.01 ± 74.87 mg/dl which was slightly lesser compared to our study 229.96 ± 66.08 mg/dl indicating the better control in the compared studies.^{11,19}

26.0% of our study subjects had abnormal funduscopy picture with either diabetic or hypertensive retinopathy (Grade I/Grade II) or both. Cveticanovic G *et al.*, reported 64.0% of the study subjects with retinopathy.¹⁷ The proportion of those with retinopathy findings are higher in the comparative study as there may be difference in the duration of diabetes among the study participants.

The Continuous Glucose Monitoring tests were carried out by Ishikawa T *et al.*, for 3.7 ± 1.2 days on an average and recorded average 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 in our current study on 0, 1 and 14 days 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 glycaemic control in the study by Ishikawa T *et al.*¹⁸

Among the 50 study subjects, 32.0% had at least one hypoglycaemic episode during the CGMS recordings and 68.0% of them did not have any hypoglycaemic episodes. In another study that investigated hypoglycaemia in Type 2 Diabetes mellitus patients for 5 days using CGMS, 49.1% of participants had at least one hypoglycaemic episode.²⁰

Our study subjects with at least 1 episode of hypoglycaemia experienced 1.1 episodes/patient/ 14 days of CGMS. Similarly, in a study by Gehlert RR *et al.*, of the patients, who experiences at least 1 hypoglycaemic episode the mean episode was 1.74 episodes/patient/ 5 days of CGMS.²⁰

Huri HZ *et al.*, reported severe hypoglycaemia (GRBS < 40 mg/dl) among 12% of subjects in their study. Similarly, 16.0% had hypoglycaemia in our study. However we recorded 50.0% of those subjects; to have severe episodes of hypoglycaemia.²¹

The mean values of FBS were less among those with hypoglycaemia and severe hypoglycaemia group compared to those without hypoglycaemia and severe hypoglycaemia in the current study which are similar to the findings on FBS by Dissanayakeet *al.*¹¹ The mean values of HbA1c were less among those with hypoglycaemia and severe hypoglycaemia compared to those without hypoglycaemia and severe hypoglycaemia. However the values were not significantly different ($P > 0.05$) indicating that that aggressive glycaemic management can be associated with increased risk for hypoglycaemia.²² Similarly in a study by Kalra S *et al.*, the hypoglycaemia scores and HbA1c values had a significant weak negative correlation.²³ Dissanayakeet *al.*, also reported patients with hypoglycaemic episodes to have a significantly higher mean age and duration of diabetes compared to those without however in the current study, the mean age and duration of diabetes were not significantly different in hypoglycaemia group compared to the group with no hypoglycaemia and also among those with severe hypoglycaemia group and no severe hypoglycaemia group as there is difference in distribution of age and duration of diabetes.¹¹

HbA1c levels and mean number of episodes of

hypoglycaemia showed significant negative correlation in the present study. Similarly in various studies, the frequency of hypoglycaemia and glycaemic control were accordingly reported was observed more frequently in intensive therapy arms of large studies like UKPDS, ACCORD, ADVANCE, and VADT.^{32,41,50,73,74} An inverse relationship was also observed between all confirmed hypoglycaemia episodes and HbA1c at endpoint.^{23,24}

CONCLUSION

More than $1/3^{\text{rd}}$ i.e., 32.0% experienced at least one episode of hypoglycaemia and 50.0% of those with hypoglycaemia had severe hypoglycaemia. Totally 16.0% experienced severe hypoglycaemia. Study subjects with at least 1 episode of hypoglycaemia experienced 1.1 episodes/patient/14 days of CGMS. Such hypoglycaemic episodes often a neglected complication needs to be paid careful attention as it can be life threatening and disabling. Hence, developing and modifying a treatment plan that is acceptable to the patient becomes important. The occurrence of hypoglycaemia and mean number of episodes of hypoglycaemia increases with decreasing levels of HbA1c.

RECOMMENDATIONS:

Careful history taking on previous history of hypoglycaemia and developing and using newer antidiabetic medications with little or no risk of hypoglycaemia can reduce the future risk of hypoglycaemia. Monitoring hypoglycaemia with the use of newly developed tools like flash glucose monitoring systems and empowering the patients in its use and making them aware of the risks and the available preventive strategies, with an individualized plan of treatment, can decrease the frequency and severity of hypoglycaemia.

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