Greater concern about hypoglycemia in Type 2 diabetics is the need of the hour—findings from a prospective, single-center, observational study

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ABSTRACT

Context: Hypoglycemia is a well-recognized adverse effect in the treatment of type 1 diabetes mellitus. For patients of type 2 diabetes mellitus (T2DM) on stabilized treatment with the current oral antidiabetic drugs, occurrence of hypoglycemia is considerably less well studied. The current study was undertaken to understand the extent of this problem in elderly Indian patients.

Objectives: Primary Objective: Assessment of incidence of hypoglycemia in patients of T2DM on stable treatment. Secondary Objectives: 1. Estimation of incidence of episodes of severe hypoglycemia in patients. 2. Correlation of presence of hypoglycemia with treatment modality.

Settings and Design: This study was conducted as an open label, single-center observational study at a multispecialty tertiary care hospital.

Materials and Methods: The study participants consisted of 50 elderly confirmed patients of either gender suffering from T2DM undergoing treatment and follow-up in the hospital for at least 12 weeks. After a brief training session and enrolment, the patients were asked to report to study site every month for next 2 months. Parameters recorded were plasma glucose levels, HbA1c levels, treatment regimen, body mass index, possible hypoglycemic episode based on symptoms and self-monitoring of blood glucose, and quality of life based on questionnaire score.

Statistical Analysis: Descriptive and other statistics were used to analyze the hypoglycemic episodes experienced by the patients for correlation with medicines and the effect of hypoglycemia on their quality of life.

Results: Total of nine hypoglycemic episodes were recorded. Severe hypoglycemia did not occur in any patient. Patient on insulin reported significantly more hypoglycemia. Quality of life is not much different in patients using insulin in T2DM.

Keywords: Hypoglycemia, insulin, quality of life, type 2 diabetes

Introduction

Diabetes mellitus (DM) is well recognized as a global healthcare burden of 21st century. The number of patients of DM have been continuously increasing over the past few decades. As per the International Diabetes Federation, there were 451 million people suffering from DM worldwide as in year 2017. This number is further projected to rise to 693 million by the year 2045.[1] Out of all the patients of DM, 90% are suffering from type 2 diabetes mellitus (T2DM).[2] India, with its second largest population in the world, is also affected very seriously by this problem. As a matter of fact, the huge number of adult diabetic patients in India has earned it the dubious title of being termed as the diabetes capital of the world. Currently, India is home to the second largest number of diabetic adults (i.e., 72 million in 2017).[3]

Even after the availability of numerous effective antidiabetic drugs and regimes, the management of diabetes is often complicated by certain barriers. One of the most important of these barriers is hypoglycemia. Hypoglycemia negatively affects patient compliance by decreasing their willingness to take medication thereby compromising the quality of life and

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the objectives of the treatment. Hypoglycemia is also linked to neuro cognitive degeneration[4,9] and detrimental changes in the cardiac electrophysiology.[9] In addition, it can be fatal when severe and leading to neurohypoglycemia.

Despite being such an important factor in the treatment of diabetes, the data available on hypoglycemia are grossly insufficient. In fact, from India, home to the second largest number of diabetics, there is negligible data on hypoglycemia. This study was designed to provide an estimate of incidence and severity of self-reported hypoglycemia in diabetic patients in real-time clinical settings at a tertiary care center in India. The outcome of this study is expected to benefit all involved in primary care of diabetes patients as hypoglycemia, if severe will first be reported and attended by the primary care physician. Additionally, the data from this study will guide the primary care physician to advise the utility of otherwise and risks of insulin use in T2DM.

**Materials and Methods**

This study was conducted as an open label, single-center, observational study at a multispecialty tertiary care hospital. Approval of the Institutional Ethical Committee was taken. The study population consisted of 50 confirmed cases of T2DM, of both genders (24 females and 26 males) undergoing treatment and follow-up in the hospital.

The inclusion criteria for the study were confirmed patients of T2DM of either gender aged between 50 and 60 years and willing to provide written informed consent. The included patients were on stabilized antidiabetic regimen for at least 12 weeks. Patients with known history of coronary artery disease, neuropsychiatric disorders, or neuro degenerative disorders were excluded from the study.

**Investigation plan**

The study was conducted over a 2-month period from June to August 2016. Patients were screened according to the inclusion and exclusion criteria. The patients who agreed to participate were asked to sign the informed consent form.

The patients after signing the informed consent form underwent an awareness and educational session regarding the identification of symptoms of hypoglycemia, possible triggers, appropriate management for hypoglycemic episodes, and the use of home glucose monitor. On enrolment, the patient data on baseline characteristics, such as demographic details, latest plasma glucose levels (both fasting and post prandial), HbA1c levels, and treatment regime were recorded on a case record form. The patients were then asked to report to study site every month for next 2 months.

The various outcome variables studied at every monthly visit included plasma glucose levels, incidence of possible hypoglycemia, body mass index (BMI) on a monthly basis, and HbA1c levels and quality of life at the end of second visit.

During the 2-month study period, the blood glucose levels (both fasting and postprandial) were checked using the available standard techniques in the hospital whenever the patient reported to the study site each month. The HbA1c levels were, however, calculated only at the end of the 2-month period in addition of the baseline reading taken at the beginning of the study.

To calculate the incidence of hypoglycemic episodes, the patients were given a glycemic study diary and asked to record any suspected hypoglycemic episode perceived. The patients were told to check and record their random blood sugar levels at that time in the glycemic study diary, using the home glucose monitor. Along with the time of the hypoglycemic episode and blood sugar levels, the patients were also asked to record the last dose of medicine, last meal, suspected triggering factor, and the management of hypoglycemic episode.

The quality of life of the patients was also assessed at each monthly visit through a EuroQol visual analog scale.[7] Their BMI was also recorded. All recorded data were analyzed using appropriate statistical tools.

**Observations and Results**

This study was done over a period of 2 months from June to Aug 2016.

Table 1 lists the baseline glycemic variables of 50 patients at the beginning of the study. The patients presented with a mean fasting and postprandial glucose of 153.42 and 222.28, respectively. The mean HbA1c was 7.97 ± 1.43.

Data from the descriptive analysis of the demographic characteristics obtained at the beginning of the study are presented in Tables 2 and 3, discriminated by gender. The age of the population studied ranged from 50 to 79 years.

Females reported higher mean blood glucose levels as compared with the male patients. The mean HbA1c levels were also higher in females than in males.

The blood glucose values of the patients at each monthly visit are depicted below in Table 3. The fasting and postprandial glucose values show a declining trend.

| Table 1: Baseline glycemic parameters |
|--------------------------------------|
| **Factor**                          | **No. of patients** | **Mean** | **Median** | **Standard deviation** |
|--------------------------------------|---------------------|----------|------------|-----------------------|
| Fasting glucose (mg/dL)              | 50                  | 153.42   | 145        | 50.11                 |
| Postprandial glucose (mg/dL)         | 50                  | 222.28   | 190        | 87.89                 |
| HbA1c (%)                            | 50                  | 7.97     | 7.9        | 1.43                  |
The HbA1c levels also showed a similar trend with the mean HbA1c at the beginning of the study being 7.97%, whereas at the end of the 2-month period, the mean HbA1c falling to 7.95%. The mean HbA1c levels in patients on insulin and in those not on insulin were not significantly different both at the start of study as well as at the end of study ($P = 0.15$ and 0.55, respectively). The readings are depicted in Table 4.

The BMI showed a fall at the end of second month. The comparative analysis of the mean BMI of the patients at the end of 1 month (24.6) and at the end of 2 months (24.49) is shown in the Table 5.

When the treatment regimens of the patients were analyzed, it was observed that 42 patients out of 50 were taking metformin, whereas 22 out of 50 were on some form of insulin therapy. The next most common drug employed was glimepiride used by 15 patients. Table 6 shows the details of antidiabetic medicines of the studied patients.

For the sake of comparison, we divided the patients in two groups – those on insulin and those who are not [Figure 1].

### Incidence of hypoglycemia

Assessment of the incidence of hypoglycemia was the primary objective of the study. During the 2-month study period, a total of nine hypoglycemic episodes were observed. This approximates to 108 hypoglycemic episodes per 100 patient years. In total, 7 patients out of 50 experienced a single episode, whereas 1 patient experienced two episodes of hypoglycemia. No incidence of severe hypoglycemia was observed. The mean random blood glucose value at the time of hypoglycemic episode was found to be 64.85 mg/dL with a standard deviation of 3.13 as depicted in Table 7. Hypoglycemia occurrence was analyzed for the patients on insulin.
Patients on insulin had significantly more incidence of hypoglycaemia as compared with those not on insulin ($P = 0.02$).

Patients on insulin had lower mean blood sugar levels as compared with those not on insulin. However, the difference is not significant ($P = 0.35$).

When the incidence of hypoglycemic episodes was correlated with the treatment modality, it was observed that out of nine episodes of hypoglycemia, six were experienced by patients who were on a combined insulin, metformin, and a second oral antidiabetic drug (it usually being a Dipeptidyl peptidase-4 (DPP-4) inhibitor like sitagliptin or vildagliptin). One episode of hypoglycemia each was observed by a patient on metformin + glimepiride, insulin + vildagliptin, and insulin alone as shown in Table 9.

The quality of life of the patients was assessed using the EuroQol visual analog scale. Majority of the patients scored their quality of life between 50 and 75, whereas less than half patients scored it over 75. Patients on insulin had marginally lower EuroQol score, which was not significantly different [Table 10].

### Table 8: Hypoglycemia in patients on and not on insulin

| Treatment Regime                  | No of episodes | Mean random blood glucose during hypoglycemic episode (mg/dL) | Standard deviation |
|-----------------------------------|----------------|---------------------------------------------------------------|--------------------|
| Hypoglycemia in patients on insulin | 7              | 62.8                                                          | 4.7                |
| Hypoglycemia in patients not on insulin | 2              | 66                                                            | 2.83               |

### Table 9: Distribution of hypoglycemic episodes amongst various drug groups

| Treatment Regime                  | No of hypoglycaemic episodes |
|-----------------------------------|------------------------------|
| Metformin alone                   | 0                            |
| Metformin + other oral drugs      | 1                            |
| Metformin + insulin               | 0                            |
| Metformin + insulin + other oral drug | 6                        |
| Insulin alone                     | 1                            |
| Insulin + other oral drug (excluding metformin) | 1                        |

### Table 10: Quality of life score of patients on and not on insulin

| EuroQoL score | Mean | Standard deviation |
|---------------|------|--------------------|
| Patients on insulin $n=22$ | 71   | 10.64              |
| Patients not on insulin $n=28$ | 74.64 | 9.61              |


drug group is on the decline, especially after the widespread use of DPP-4 inhibitors.

There is meagre literature on the incidence of hypoglycemia, especially in the Indian settings. Despite a meticulous search for literature, we could not find many studies wherein hypoglycemia has been the primary objective of the study. In view of the above, it was considered worthwhile by us to plan a study wherein hypoglycemia is studied as a primary endpoint. We made an endeavor to study incidence of severe hypoglycemia in our patients over a 2-month study period. One recent Indian study placed the incidence of severe hypoglycemia at 23%.[9]

The study population in our study were elderly. This age profile matches with our inclusion criteria. The reason for selecting patients from this age group was to ensure better understanding of the disease and treatment regimens. Elderly patients are at a greater risk of hypoglycemia, and therefore, the incidence recorded in our study is representative of the “at risk” group of patients. In the elderly, hypoglycemia is under diagnosed and underreported.[9] Hypoglycemia occurring in elderly patients make them prone to development of dementia, which, in turn, increases the risk of hypoglycemia further.[10]

A close look at the blood sugar and HbA1c levels reveals that despite medication, the patient's blood sugar levels remained significantly high. It is not entirely new finding though surprising to us.[11] The slight improvement in glycemic control may be attributed to the patient's recruitment to the study when they become more compliant to treatment as well as become more conscious of their diet.[11] This reason is plausible, more so because there is a trend in fall in BMI also.

Analysis of the antidiabetic regimes reveals that the patients are being treated with metformin predominately, supplemented largely by DPP-4 inhibitors, and much lesser numbers by sulfonylureas and insulin. It is surprising to note that still majority of the patients are not achieving the expected euglycemia. The reasons could be improper compliance with treatment, or dietary indiscretion, both vitiating the metabolic condition.

In the entire study period of 2 months, a total of nine hypoglycemia episodes were documented in eight patients. Majority of those episodes occurred in patients who were on insulin in addition to oral antidiabetic drug. The mean random blood sugar levels at the time of hypoglycemia was 64.85 mg/dL, which correlates well with the self-detection and management by patients suffering hypoglycemia episodes. It is evident therefore from our study that starting the patients of T2DM on insulin concurrently enhances the risk of hypoglycemia.13 Our study further confirms what is

### Discussion

In the treatment of DM, hypoglycemia is always a concern. In T2DM, treated mostly with oral drugs, the concern is lesser than that of Type 1 DM. Among the oral drugs, the maximum risk of hypoglycemia is with sulfonylureas, though the use of this
well known, but if did not achieve statistical significance, probably because of small sample size. It can also be assumed that a stricter and scrupulous control of blood sugar levels would have caused much more incidences of hypoglycemia.[14] Out of 28 patients who are on OHAs alone, only one suffered hypoglycemia. Most of the patients who were on metformin with a DDP-4 inhibitor stayed free of hypoglycemia.

Our study indicates that putting the patients on insulin improves their glycemic control, though due to the small sample size, statistical significance was not achieved. Putting a patient on insulin increases documented hypoglycemia.

We tried to find the effect of hypoglycemia on the quality of life of the patients. It is noted that the patients who suffer hypoglycemic episodes rated their quality of life lower in comparison to patients free from hypoglycemia. One of the reasons for reluctance or delay in starting patients of T2DM on insulin is because of QOL concerns.[15] Our study indicates otherwise. Hence, a more liberal view and early institution of insulin therapy may help patients achieve their treatment goals better.

There are a few limitations to our study. Being an open label study and part of the assessment based on patient recall, it is likely to be affected by bias. The number of patients has been kept low and duration of 2 months, keeping the infrastructural constraints of the study in mind. A larger number of patients followed for a longer duration will surely throw more light on the matter of hypoglycemia in patients of T2DM.

**Conclusion**

The present study investigated the incidence of hypoglycemic episodes in 50 patients of T2DM on a stable treatment with oral antidiabetic drugs with or without insulin. It was found in our study that 108 episodes of hypoglycemia occurred in 100 patient years. Hypoglycemic episodes were more in patients who were on insulin therapy along with oral drugs. Patients not on insulin still need to be sensitized about hypoglycemia and their blood sugar level also be monitored when they experience symptoms of hypoglycemia. It is also observed that patients even with proper treatment did not reach euglycemic levels. There was no correlation of hypoglycemia with any particular oral antidiabetic drug group.

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**Conflicts of interest**

There are no conflicts of interest.

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