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ORIGINAL ARTICLE

Self reported hypoglycemia in patients with type 2 diabetes mellitus taking oral anti-diabetics

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Abstract

Objective To determine the proportion of patients of type 2 Diabetes taking oral antidiabetics with self reported hypoglycemia and its causes.

Background Hypoglycemia, an acute complication of diabetes mellitus is not only responsible for recurrent morbidity but also can lead to permanent brain damage or fatality if not recognized and treated in time. Also, hypoglycemia prevents achieving glycemic targets in diabetic patients.

Methods Cross-sectional observation study of 70 patients of type 2 diabetes on oral anti-diabetics was conducted at Lok Nayak Hospital to determine the proportion of patients with self reported hypoglycemia and also to find out the various causes of hypoglycemia by subjecting them to a structured questionnaire. Hypoglycemia was considered when patient experienced at least one symptom, at least 2–3 times in last one month and symptom(s) were relieved by consuming sugar/meal.

Results 38.6% of the study subjects had hypoglycemia, out of which 92.59% patients had symptomatic hypoglycemia. Out of the patients experiencing hypoglycemia, 32% had severe episodes, 12% visited the hospital and 48% had more than 5 episodes per month. Dizziness was the commonest reported symptom (64%), followed by palpitations (52%). Attributed causes of hypoglycemia were missing meal (64%), drugs other than oral anti-diabetics (44%), sulfonylureas (44.2% in patients taking vs. 26.9% in patients not taking sulfonylurea), comorbidities (41% with vs. 22.4% without comorbidities) and lower socioeconomic status. One-third of patients experiencing were checking blood glucose levels during the symptoms. Highest prevalence of hypoglycemia was seen with $HbA_{1c} < 6.5\%$ (p-value 0.04 when compared with subjects with $HbA_{1c} \geq 6.5\%$), followed by $\geq 8\%$ and least in 6.5–7.9%.

Conclusions Lower prevalence of hypoglycemia in our study compared to other similar studies could be because of non-inclusion of patients on insulin in our study. High prevalence of multiple episodes justify the fact that hypoglycemia begets hypoglycemia. Hypoglycemia progressively increased as socioeconomic status changed from higher to lower, possibly due to non-availability of glucometer and lack of information. U-shaped correlation of hypoglycemic events was found with HbA_{1c} levels.

Keywords Type 2 diabetes mellitus · Hypoglycemia · Oral anti-diabetics

Introduction

The major complication which prevents achieving glycemic targets in diabetes, both type 1 and type 2 diabetes, is hypoglycemia. Also, hypoglycemia causes recurrent morbidity in patients with diabetes, especially type 1 diabetes and advanced type 2 diabetes. Prolonged hypoglycemia or delay in its treatment can lead to permanent brain damage (may lead to brain death) and sometimes can be fatal [1].

Whipple's triad is usually used to document hypoglycemia. It was first described in 1938 [2]. It includes the following three criteria:

- Symptoms, signs or both consistent with hypoglycemia.
- A low plasma glucose concentration measured with a precise method.
- Relief of the symptoms or signs after the plasma glucose level is raised (usually by administration of oral or intravenous glucose) [1].

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According to ADA 2022, hypoglycemia is currently classified as level 1, 2 and 3.

- Level 1 hypoglycemia: measurable blood glucose concentration < 70 mg/dL (3.9 mmol/L) and ≥ 54 mg/dL (3.0 mmol/L). A blood glucose concentration of 70 mg/dL is recognized as the threshold at which neuroendocrine responses to falling blood glucose develops in normal individuals.
- Level 2 hypoglycemia: blood glucose concentration < 54 mg/dL. This is the threshold at which neuroglycopenic symptoms occur.
- Level 3 hypoglycemia: is defined as a severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. There is no specific blood glucose concentration specified for level 3 hypoglycemia [3].

The symptoms of hypoglycemia are of two types:

1. Neurogenic (or autonomic) symptoms: They occur due to physiological autonomic nervous system activation due to hypoglycemia. They are further of two types:
    - Adrenergic symptoms: they are catecholamine-mediated and include anxiety, tremors and palpitations. They occur due to norepinephrine released in the target tissues from the post ganglionic sympathetic nerve fibres and due to adrenaline released from adrenal medulla.
    - Cholinergic symptoms: They are acetylcholine-mediated and include hunger, paraesthesias and sweating.
2. Neuroglycopenic symptoms: they occur directly due to insufficient brain blood glucose supply. They include confusion, weakness, fatigue, warmth sensation, behavioural changes, seizures, coma and ultimately death [4].

There are a large number of patients, who experience symptoms of hypoglycemia, but they don't report them to their doctor and hence their hypoglycemic episodes remain unreported. Since hypoglycemia can have serious repercussions and previous history of hypoglycemic episodes predisposes the patient to developing hypoglycemia again, it is important to identify such patients whose hypoglycemic episodes go undetected [5].

Most of the studies on hypoglycemia have focused on patients using insulin, there are only a limited number of studies on patients using oral anti-diabetics.

This study was done to determine the proportion of patients of type 2 diabetes mellitus taking oral anti-diabetics with self reported hypoglycemia and to find out the various cause/ causes of the hypoglycemia.

Materials and methods

This study was a cross-sectional observational study conducted at Maulana Azad Medical College and Associated Hospital Lok Nayak Hospital in the Department of Medicine, New Delhi, over a period of 1 year.

All patients with type 2 diabetes mellitus on oral anti-diabetics with duration of diabetes of more than 5 years were included in this study. Diagnosed cases of diabetic nephropathy, co morbid illness like chronic liver disease, chronic kidney disease (other causes), malignancy, patients with sepsis, gestational diabetes mellitus were excluded.

70 patients were randomly picked up from diabetic/ medicine out- patient department. All patients were administered a structured questionnaire by the investigator in which all possible symptoms of hypoglycemia were included and probable causes were included. Patients who experienced at least 1 symptom at least 2–3 times in the last 1 month and whose symptoms were relieved after consuming sugar or a meal were considered to have had a hypoglycemic episode.

The following laboratory investigations were sent for the patients:

1. Blood sugar levels – fasting and post-prandial.
2. HbA_{1c}.

Before the start of the main study, the questionnaire was validated in a pilot study in 10 patients.

Statistical analysis

The collected data were transformed into variables, coded and entered in Microsoft Excel. Data were analyzed and statistically evaluated using SPSS-PC-25 version. Normal distribution of different parameters was tested by the Shapiro-Wilk normality test. Quantitative data was expressed in mean ± standard deviation. Qualitative data were expressed in frequency and percentage and statistical differences between the proportions were tested by chi square test or Fisher's exact test. Univariate analysis was done to find risk factors for hypoglycemia & odds ratio was calculated to see strength of association. *p*' value less than 0.05 was considered statistically significant.

Results

The baseline characteristics of the patients are shown in Tables 1 and 2. Mean age of the study population was 53.27 ± 10.08 years. Most common age group was 40–59 years (65.7%) followed by ≥ 60 years (27.2%). 55.7%

Table 1 Baseline characteristics of the patients

	No. ($n=70$)	Percentage (%)
Age Group (years)		
<40	5	7.1
40–59	46	65.7
>/=60	19	27.2
Gender wise distribution		
Male	31	44.3
Female	39	55.7
Duration of diabetes (years)		
5–10	57	81.5
1 1–15	8	11.4
>15	5	7.1

Table 2 Baseline characteristics of patients

	No. ($n=70$)	Percentage (%)
Socioeconomic status		
Upper	1	1.4
Upper middle	8	11.4
Lower middle	8	11.4
Upper lower	27	38.6
Lower	26	37.2
Comorbidities		
Hypertension	36	51.4
Dyslipidemia	30	42.9
none	9	12.8
HbA_{1c}(%)		
<7	17	24.3
>/=7	53	75.7
Treatment status		
Single drug	6	8.6
Multiple drug	64	91.4

of the study population were females and 44.3% were males. Mean duration of DM was 8.66 ± 4.81 years with minimum duration of 5 years and maximum of 25 years. Most patient had duration of diabetes 5–10 years (81.5%), followed by 11–15 years (11.4%) and > 15 years (7.1%).

Most of the patients in our study population belonged to upper lower (38.6%) and lower (37.2%) socioeconomic status, followed by upper middle (11.4%), lower middle (11.4%) and upper (1.4%) socioeconomic status. The socioeconomic status was calculated by Modified Kuppuswamy scale 2021. 87.2% of the study population had one or more comorbidities. 12.8% did not have any comorbidty. The most common comorbidity was hypertension (51.4%), followed by dyslipidemia (42.9%), coronary artery disease (8.6%), dementia (8.6%), hypothyroidism (7.1%), diabetic neuropathy (7.1%). Mean HbA_{1C} was 8.95 ± 2.43. 24.3% patients had $HbA_{1c} < 7\%$ (good glycemic control), whereas 75.7% patients had $HbA_{1C} \geq 7\%$ (poor glycemic control).

91.4% patients were on multiple oral antidiabetic drugs for management of diabetes, whereas 8.6% patients were on a single oral antidiabetic drug for management of diabetes. Metformin was used by 100% patients. Apart from that, commonly used drugs included glimeperide (57.1%) and vildagliptin (51.4%). Other drugs used by patients in different combinations were voglibose, dapagliflozin, gliclazide, pioglitazone, teneligliptin, linagliptin, canagliflozin and remogliflozin. None of the patients taking insulin were included in this study. 61.4% of the patients were taking sulfonylureas for management of diabetes which included glimeperide and gliclazide.

The symptoms of hypoglycemia encountered (Fig. 1) were tremors, sweating, palpitations, paraesthesia, hunger, behavioral changes, confusion, fatigue, dizziness, blurring of vision, headache, nightmares, loss of consciousness, transient focal neurological deficit alone or in various combinations. Dizziness was the most common symptom (64%), followed by palpitations (52%), sweating (48%), blurring of vision (48%), paresthesia (48%) and tremors (40%) in patients experiencing symptomatic hypoglycemia.

Out of the 70 study subjects with diabetes screened for hypoglycemia, symptomatic hypoglycemia was found in 25 patients (35.7%). In the 70 study subjects screened, 43 were found to have symptoms of hypoglycemia, but these symptoms were relieved by intake of sugar or meal in only 25 of these patients and hence, 25 patients were considered to have symptomatic hypoglycemia. Thus, the proportion of patients having symptomatic hypoglycemia in our study was 35.7%. The low blood glucose was confirmed by glucometer in 9 (12.8%) patients. Apart from this, 6 patients (8.6%) had documented hypoglycemic episodes on routine monitoring but were asymptomatic at that time (asymptomatic hypoglycemia). 4 patients had symptomatic as well as asymptomatic hypoglycemia (5.7%). Hence, total 27 patients had symptomatic or asymptomatic hypoglycemia (38.6%) (Fig. 2).

The most common suspected cause of hypoglycemia in this study was found out to be due to skipped meals, which was seen in 64% of the patients having symptomatic hypoglycemia. Other attributed causes in the decreasing order of their frequency were found to be due to use of drugs other than oral antidiabetics (44%), strict glycemic control (28%), dementia (24%), weight loss (20%), excessive physical activity (12%), recent alcohol use (4%) and recent increase in dose or addition of a new oral antidiabetic drug (4%) (Fig. 3).

22.8% of the study subjects had 2–4 episodes in the last 1 month, 8.6% had 5–7 episodes and 22.8% had > 7 episodes. Out of the patients in whom symptoms relieved by taking sugar or meals (having symptomatic hypoglycemia), 52% had 2–4 episodes/ month, 16% had 5–7 episodes/ month

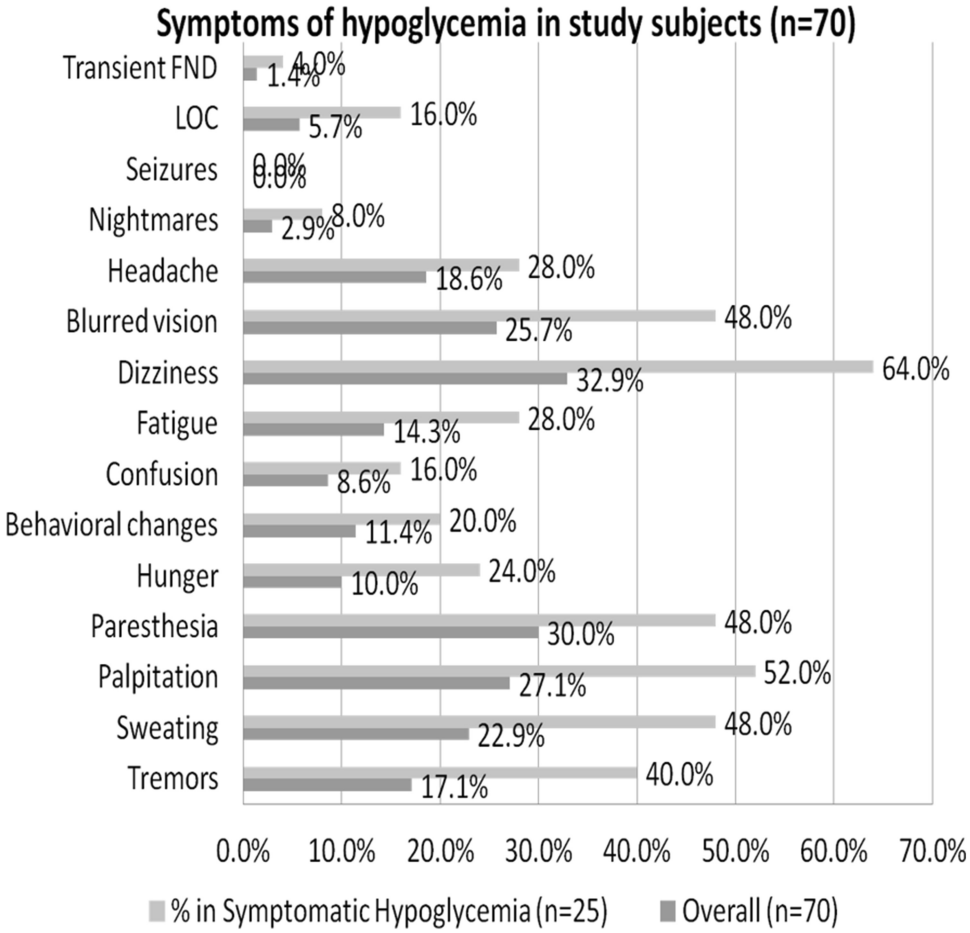

Fig. 1 Symptoms of hypoglycemia in study subjects

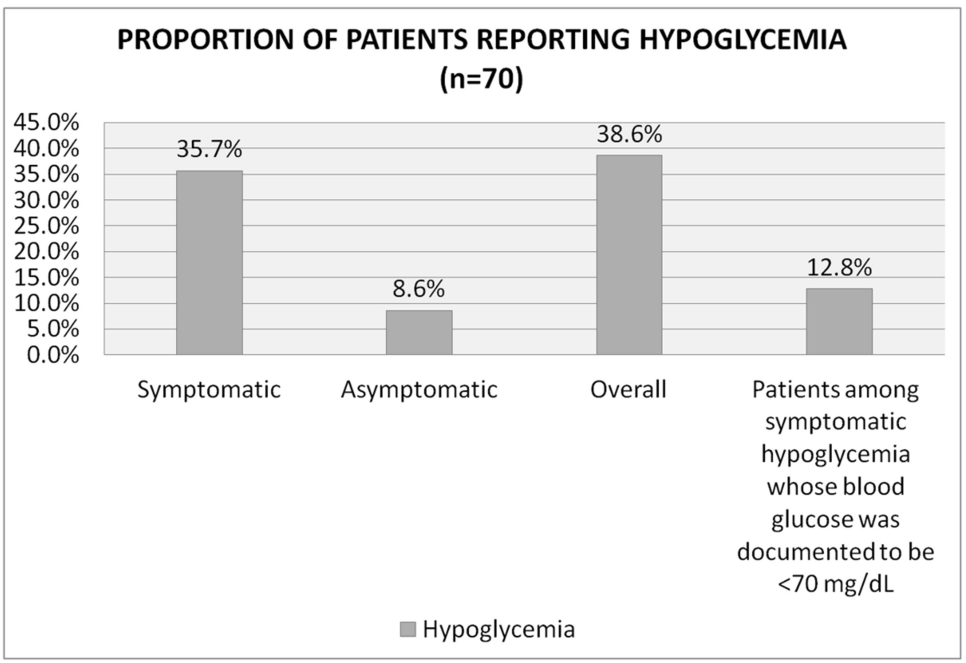

Fig. 2 Proportion of patients reporting hypoglycemia

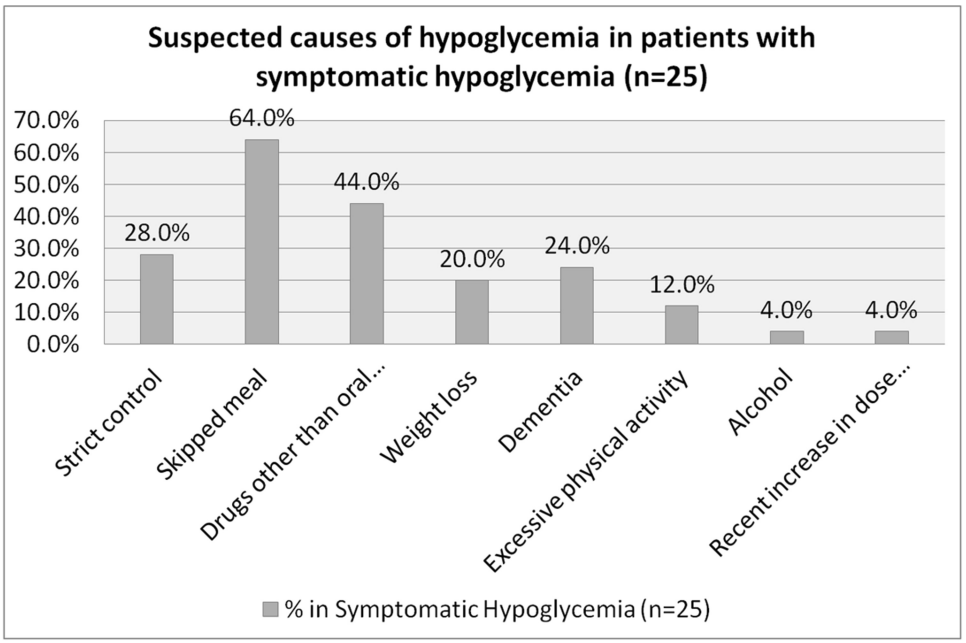

Fig. 3 Suspected causes of hypoglycemia in patients with symptomatic hypoglycemia

and 32% had > 7 episodes/ month and 5 patients out of these (20%) had symptoms daily.

Out of the patients having symptoms of hypoglycemia, only 34.9% checked their blood glucose level during the symptoms. Among those who checked blood glucose in our study, 20% had blood glucose < 54 mg/dL, 40% had blood glucose 54–70 mg/dL and 40% had blood glucose > 70 mg/dL (relative hypoglycemia). Overall 9 people (20.9%) among having symptoms needed someone's assistance during the symptoms. 8 (32%) patients among those reporting symptomatic hypoglycemia required assistance for treatment of hypoglycemia during the episode and hence were reported to have level 3 or severe hypoglycemia. 3 (12%) of the patients reporting symptomatic hypoglycemia visited the hospital for their symptoms.

Maximum prevalence of hypoglycemia was seen in the age group 40–59 years (45.7%), followed by in the age group ≥ 60 years (26.3%) and least in < 40 years (20%), but this difference was not statistically significant (*p*-value 0.23). There was no sex predisposition for hypoglycemia in our study. The prevalence of hypoglycemia in males was 38.7% and in females was 38.5%.

More hypoglycemic events were seen in lower (42.3%) and upper lower (40.7%) socioeconomic status as compared to upper middle (25%) and lower middle (37.5%) socioeconomic status. No hypoglycemic events were recorded in our single case of upper socioeconomic status. Hence, in our study, the risk of hypoglycemic events progressively increased as the socioeconomic status changed from upper to lower class, though this was not statistically significant (*p* value- 0.83).

The prevalence of hypoglycemia in our study was compared with HbA_{1c} levels (Fig. 4). The percentage of hypoglycemic events were maximum in two extremes, 61.5% in patients with $HbA_{1C} < 6.5$, followed by 35.7% in patients with $HbA_{1C} \geq 8$, whereas they were least in patients with relatively good glycemic control, 20% and 27.3% in patients with HbA_{1C} 6.5–6.9 and 7–7.9 respectively, but these results were not statistically significant (*p*-value 0.14). Our study showed statistically significant higher number of hypoglycemic events in patients with $HbA_{1c} < 6.5$ (61.5%) as compared to $HbA_{1C} \geq 6.5$ (32.8%) with odds ratio of 4.10 (*p*-value 0.04) (95% CI- 1.09 to 15.36).

In this study, it was found that prevalence of hypoglycemia was more in patients on single oral anti-diabetic drug (50%) as compared to patients on multiple oral anti-diabetic drugs (37.5%) but this difference was not statistically significant (*p*-value 0.67) with an odds ratio of 1.66 (95%CI:0.31–8.92). The prevalence of hypoglycemia was more in patients taking sulfonylureas (44.2%) compared to patients not taking them (29.6%) but this difference was not statistically significant. (*p*-value 0.22) and an odds ratio of 1.88 was seen (95%CI: 0.67–5.22).

The prevalence of hypoglycemia in our study was more in patients with a comorbidity (41.0%) as compared to patients without comorbidity (22.2%), but this difference was not statitistically significant (*p*-value 0.46) odds ratio 2.43 (95%CI:0.46–12.68). The comorbid conditions in our study in various combinations were predominantly hypertension (51.4%), dyslipidemia (42.9%), dementia (8.6%), diabetic neuropathy (7.1%), coronary artery disease (8.6%) and hypothyroidism (7.1%).

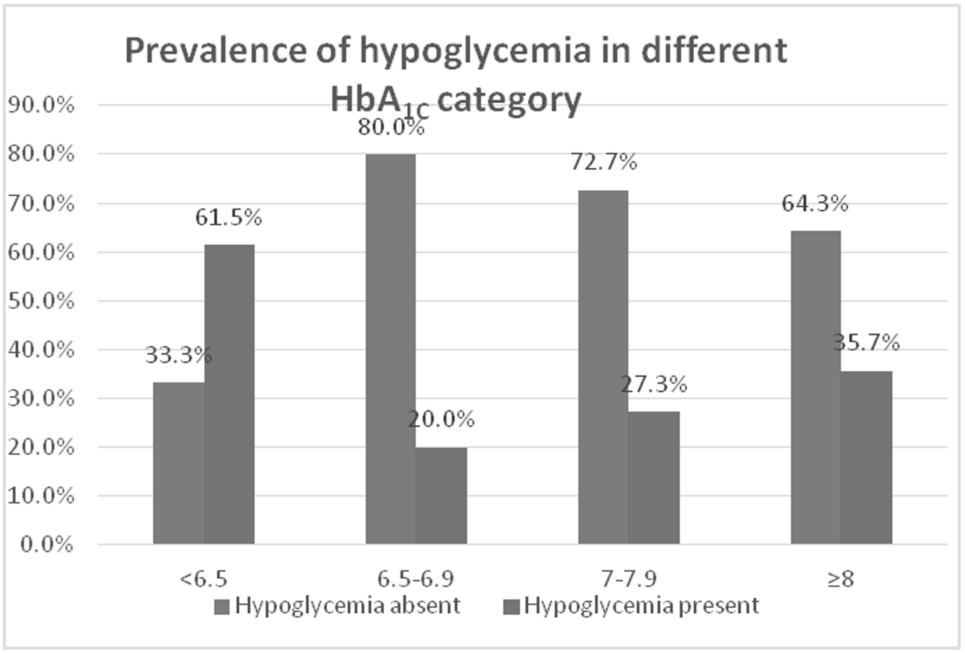

Fig. 4 Comparison of prevalence of hypoglycemia with HbA_{1c} levels

In our study, it was also found that patients taking drugs other than antidiabetic medications like aspirin, ACE inhibitor/ARB, beta blockers, alcohol, non-steroidal anti-inflammatory drugs, reported slightly more hypoglycemic events (40%) as compared to patients not taking any of these drugs (37.5%) but this difference was not statistically significant (*p*-value 0.83). None of our patients were on any other common drugs known to be associated with hypoglycemia.

Discussion

This cross-sectional observational study was done in Lok Nayak Hospital with approval from institutional ethics committee. The study participants were those who attended the medicine and diabetic outdoor clinic.

Our study comprised of 70 participants from the age group 34–79 years, most of them were of the age group 40–59 (65.7%) years of age with mean age 53.27 ± 10.08 years. Gender-wise distribution was males 44.3% and females 55.7% in the studied population. Our study sample was of mixed pattern when classified according to occupational status. It was found that retired/ homemakers were 55.7%, sitting workers were 24.3%, routine workers were 10% and mechanical workers were 10%. Majority of subjects had diabetes for duration of 5–10 years (81.5%). The mean duration of diabetes was 8.66 ± 4.81 years with minimum duration of 5 years and maximum of 25 years. The study population catered to all socioeconomic status with maximum patients belonging to upper lower socioeconomic status (38.6%).

43 out of the 70 patients had symptoms of hypoglycemia and these symptoms were relieved in 25 of these patients after intake of sugar or meal and hence, 25 were included in patients having symptomatic hypoglycemia. Thus, the proportion of patients having symptomatic hypoglycemia in our study was 35.7%. The low blood glucose was confirmed by glucometer in 9 (12.8%) patients. This was because most of our patients belonged to lower and upper lower socioeconomic status (75.8%) and hence could not afford a glucometer. This can also be explained by the fact that most of our patients did not have the knowledge of hypoglycemia and its symptoms (67.14%) and hence did not check the blood glucose levels when they had symptoms. Apart from this, 6 patients (8.6%) had asymptomatic hypoglycemia. 4 patients had symptomatic as well as asymptomatic hypoglycemia (5.7%). Hence, total 27 patients had symptomatic or asymptomatic hypoglycemia and the proportion of patients having hypoglycemia in this study was found out to be 38.6%. The above findings were similar to a study conducted in rural health centre in South India by V. Samya et al., in which 57.44% patients reported hypoglycemia [6]. The slightly less proportion of patients having hypoglycemia in our study can be explained by the fact that patients taking insulin were excluded in our study which is known to be associated with more hypoglycemic events. In a study conducted by Vanishree Shriraam et al., patients who were on insulin along with OHAs were at more risk of having hypoglycemia (36%) as compared to patients taking only OHAs (19.6%) [7]. According to a systematic review and meta-analysis of population based studies, the prevalence of hypoglycemia in patients with type 2 diabetes was 38%

in patients taking sulfonylureas and 73% in patients taking insulin [8].

The symptoms encountered during hypoglycemic episodes were tremors, sweating, palpitations, paraesthesia, hunger, behavioural changes, confusion, fatigue, dizziness, blurring of vision, headache, nightmares, loss of consciousness, transient focal neurological deficit alone or in various combinations. Dizziness was the most common symptom (64%), followed by palpitations (52%), sweating (48%), blurring of vision (48%) and tremors (40%). This was similar to a study conducted in South India by V. Samya et al., in which the most common symptoms were dizziness (72.3%) followed by sweating (44.2%) [6]. Similar symptom profile was also found in a study conducted by Vanishree Shriraam et al., in which the second most common symptom of hypoglycemia was dizziness (74%) [7]. In an online, opt-in survey in United Kingdom, the common symptoms of hypoglycemia were found to be trembling (55.3%), dizziness (53.6%) and sweating (38.6%) [9].

The most common suspected cause of hypoglycemia in this study was found out to be due to skipped meals, which was seen in 64% of the patients having symptomatic hypoglycemia. Other attributed causes in the decreasing order of their frequency were found to be due to use of drugs other than oral antidiabetics (44%), strict glycemic control (28%), dementia (24%), weight loss (20%), excessive physical activity (12%), recent alcohol use (4%) and recent increase in dose or addition of a new oral antidiabetic drug (4%). These findings were similar to other studies. The most common cause of hypoglycemia reported in a hospital based cross-sectional study conducted by Vanishree Shriraam et al. was missed or delayed food intake, reported by 90.6% patients who had hypoglycemia [7]. Most common self reported cause of hypoglycemia in a cross-sectional study conducted by V. Samya et al. was missed or delayed food intake, seen in 90% patients [6]. In an online, opt-in survey conducted in United Kingdom the hypoglycemic episodes were commonly attributed to delayed meals (29.6%), irregular or too few carbohydrate intake (24.8%), skipped meals (20.4%), too much exercise (15.6%) and stress (13.2%) [9]. Missed meal was also the most common cause of hypoglycemia found in a retrospective, cross-sectional analysis study conducted by Christopher D. Miller et al., and was found to be the cause in 80.9% patients [10]. In the SAVOR-TIMI 53 trial which compared effects of saxagliptin or placebo, added to standard care, the most frequent precipitating event of hypoglycemia in both arms was missed meal (50.7% in saxagliptin therapy and 48.7% in placebo arm) [11].

The prevalence of hypoglycemia in our study was compared with HbA_{1c} levels and was found to have a U-shaped pattern. The percentage of hypoglycemic events were maximum in two extremes, 61.5% in patients with $HbA_{1C} < 6.5$, followed by 35.7% in patients with $HbA_{1C} \geq 8$, whereas they were least in patients with relatively good glycemic control, 20% and 27.3% in patients with HbA_{1C} 6.5–6.9 and 7–7.9 respectively. Even though these results were not statistically significant, these results were similar to The Diabetes and Aging Study in which the relationship between severe hypoglycemic episodes and HbA_{1c} was found to be U-shaped and the percentages of hypoglycemic episodes in HbA_{1c} groups of <6, 6–6.9, 7–7.9, 8–8.9, ≥ 9 were 11.5%, 9.3%, 10.6%, 11.5% and 13.8%, respectively [12].

Our study showed statistically significant higher number of hypoglycemic events in patients with $HbA_{1c} < 6.5$ (61.5%) as compared to $HbA_{1C} \geq 6.5$ (32.8%) with odds ratio of 4.10 (p-value 0.04) (95% CI- 1.09 to 15.36). These findings were similar to the ACCORD study, in which patients with intensive therapy ($HbA_{1c} < 6.0\%$) and standard therapy (HbA_{1C} 7.0 to 7.9%) had hypoglycemia rates requiring assistance of 16.2% and 5.1% respectively, and hypoglycemia rates requiring medical assistance of 10.5% and 3.5% respectively (p-value < 0.001) [13]. It was also found in the ADVANCE trial that incidence of severe hypoglycemia in the intensive control patients (mean HbA_{1c} 6.5%) was 2.7% as compared to 1.5% in the standard control patients (mean HbA_{1c} 7.3%) and the difference was statistically significant [14].

Limitations

1. Sample size of this study was small as the study was being done during COVID-19 pandemic time period when the outpatient clinics were intermittently shut down due to the pandemic in our Lok Nayak Hospital.
2. It was a cross-sectional study and follow up of the patients was not possible.
3. Most of the patients belonged to lower socio-economic status and hence, could not afford a glucometer and also did not understand the importance of self-monitoring of blood glucose, and hence the blood glucose value could not always be documented when the patients had symptoms of hypoglycemia.

Conclusion

Dizziness and palpitations were the most common symptoms of hypoglycemia in our study subjects and these otherwise common symptoms should not be ignored in diabetic patients on medications. Multiple episodes of hypoglycemia were seen quite frequently justifying the saying that hypoglycemia begets hypoglycemia. So, even a single episode of hypoglycemia should not be taken lightly. Self monitoring of blood glucose needs to be emphasized not only in patients taking insulin for glycemic management, but also in patients

taking oral antidiabetic agents as they are also associated with hypoglycemia.

Declarations

Ethical clearance The study was conducted after taking approval from Institutional Ethics Committee of Maulana Azad Medical College dated 14/01/2021 vide letter no. F.1/IEC/MAMC/(82/10/2020/No.64. Each subject was given a consent form to fill. Subjects were explained the purpose of study and his/ her right to quit at any time without giving the reasons. Patient's information was dealt with confidentiality. Any abnormality detected during the screening of subjects was appropriately managed.

Conflicts of interest There are no conflicts of interest to report.

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