

Study of Association of Hypoglycemic Episodes to Various Potential Risk Factors among Type 2 Diabetes Mellitus (T2DM) Patients

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DOI: [10.36348/sjm.2023.v08i02.004](https://doi.org/10.36348/sjm.2023.v08i02.004)

| Received: 07.01.2023 | Accepted: 13.02.2023 | Published: 28.02.2023

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Abstract

Aim: Hypoglycemia is a major barrier to achieving proper glycemic control in type 2 diabetes mellitus patients. This study aims to document the incidence of hypoglycemia in type 2 diabetes mellitus patients and assess its association with potential risk factors. **Methods:** This is a cross-sectional study conducted in the Medicine outpatient department of a tertiary care hospital in Gujarat, India. A total of 174 patients with confirmed type 2 diabetes mellitus were interviewed using a pretested semi-structured questionnaire- Stanford Hypoglycemia Questionnaire. Patients with hormone-secreting disorders or pregnant women were excluded. Another questionnaire recorded various potential risk factors. Statistical test for proportions was used to assess the association between incidence of hypoglycemia and the risk factors. **Results:** Majority (92.5%) had a positive history of hypoglycemic events. A significant association was established between frequency of hypoglycemia, and duration of disease, BMI, sedentary lifestyle and insulin usage. Regularity of food intake, drug compliance and alcohol consumption were not significant factors. **Conclusion:** Increased incidence of hypoglycemia was significantly associated with pharmacological and non-pharmacological factors including insulin therapy, sedentary lifestyle, obesity, and chronicity of the disease. This knowledge shall help medical practitioners to strategize individualized care and maintain glycemic control in diabetic patients.

Keywords: Diabetes, hypoglycemia, obesity, Insulin, Lifestyle, Body Mass Index (BMI).

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INTRODUCTION

The increased prevalence and profound consequences of diabetes, with its associated chronic morbidities including blindness, kidney failure, heart attack and stroke, remain a major global threat. According to National Family Health Survey – 5 (NFHS-5) survey, 13.5% of women and 15.6% of men surveyed, either had high blood sugar or were taking medications to reduce the blood sugar level [1]. Effective management of diabetes principally focuses on lowering blood glucose level with medications and lifestyle modifications. However, one of the most common and challenging issue with maintaining a strict glycemic control is the increased incidence of iatrogenic hypoglycemia [2-5]. Dizziness usually appears as the first sign of hypoglycemia followed by weakness and fall. Whipple's triad is an effective

indicator of hypoglycemia [6]. Untreated cases can complicate into seizures, loss of consciousness and even death. On the other hand, lack of glycemic control results in rapid development of micro vascular and macro vascular complications.

Prevention of such crisis can be attained by proper education and awareness of patients and their family, routine health checkup and adherence to doses schedule. Hypoglycemia and its distressing symptoms of giddiness, anxiety, depression severely impairs quality of life, affects individuals' productivity and imposes financial burden for the patient and their family [2, 3]. Hypoglycemia is a condition characterized by documented blood glucose values less than 70 mg/dl in fasting state or less than 100 mg/dl when tested at any random time. The patients with type 2 diabetes

experience considerable hypoglycemic events as compared to patients with type I diabetes [9, 12]. The incidence of hypoglycemia in patients with type II diabetes has been approximately 1637 episodes for 100 patient years [12]. Yet the necessity to identify associated risk factors remains high.

Hypoglycemia is common in type-2 diabetes mellitus (T2DM) patients and is much more prevalent in older patients, individuals with comorbidities, and those on insulin therapy or Sulfonylurea medications. A study conducted in rural population in India has estimated the prevalence of hypoglycemia to be 57.44% with about one-tenth of them experiencing severe hypoglycemia [4]. Although there are other studies recognizing increased frequency of hypoglycemia episodes in T2DM patients, it is important to have epidemiological data pertaining to specific sub-population belonging to the diverse ethnic groups of India. It is also highly essential to prevent the hypoglycemia associated morbidity and mortality. As an initiative, this study aims to evaluate the frequency of hypoglycemia episodes in T2DM individuals attending a tertiary care hospital in Gujarat state of India and identify the contributing risk factors to help strategize preventive control measures.

METHODOLOGY

This is a cross sectional study conducted at a tertiary care hospital in the state of Gujarat, India for duration of four months. The study was approved by the institutional ethical committee (IEC) of the tertiary care hospital. The study was conducted from April 2019 to December 2019. All patients with confirmed T2DM undergoing treatment for diabetes in the Medicine outpatient department (OPD) at Sir Sayajirao General Hospital (SSG) Hospital, Vadodara were enrolled for the study after a written and informed consent was obtained. Pregnant women, patients suffering from Cushing's syndrome and other comorbidities such as hypertension, pancreatic cancer or acute pancreatitis, thyroid disorders or having unusual hormone-secreting tumor were excluded from the study. Based on analysis from pilot data, patients experiencing hypoglycemia events were 70%. The study sample size was estimated as 174, based on the p-value and error rate of 10%.

On an average, 250 patients visit Medicine OPD every week. A total of 192 patients were interviewed and 174 were selected who met the inclusion criteria. Considering 16 weeks, The patients who met the inclusion criteria were selected randomly by generating computerized random numbers and asked questions pertaining to the variables included in the study. The enrolled patients were interviewed on the day of their visit using a pretested semi-structured questionnaire i.e., the Stanford Hypoglycemia Questionnaire regarding presence of symptoms. A separate questionnaire was used to record possible hypoglycemic risk factors. Their weight and height

were also recorded at the time of interview for calculation of body mass index (BMI).

The hypoglycemia questionnaire was filled in by the researcher upon interrogating the patient, the symptoms experienced by the patient and their frequency were found out and hypoglycemic episodes experienced by the patient were recorded. After taking written informed consent, a separate questionnaire was used to record the possible hypoglycemic risk factors present in the patients. The questions were asked questions in the patients' vernacular language and responses were recorded.

Since the study does not involve any intervention or interfered with the patients' treatment, the process did not pose any potential risk or harm to the patients. The questionnaire did not involve any confidential issues and privacy was ensured while conducting the interview. The interview took approximately 15-20 minutes for each patient, and the local language of area was the preferred common medium of interview. Questions were asked to the subjects according to the Stanford Hypoglycemia Questionnaire (See Table 1).

According to this questionnaire, the patient must respond positively to at least 1 of the given 12 criteria for the symptoms for it to be considered as a case of hypoglycemia. A separate questionnaire (See Table 2) was used for recording possible hypoglycemic risk factors like duration, drug compliance and type of medication, BMI, alcohol addiction, physical activity, and diet.

The risk factors with which hypoglycemic episodes were associated were expressed in proportion as percentage (%). The prevalence rate of hypoglycemia among diabetic patients was estimated.

DATA ANALYSIS AND STATISTICAL METHODS

The data was entered and analyzed by using Microsoft Excel 2010. Chi-square test was used to see the association between hypoglycemia and risk factors at 95% confidence interval (CI). The symptoms of hypoglycemia were recorded in proportion as percentage (%) as per Stanford Hypoglycemic Questionnaire (SHQ).

OPERATIONAL DEFINITIONS

Hypoglycemia: A condition characterized by documented blood glucose values less than 70 mg/dl in fasting state or less than 100 mg/dl when tested at any random time.

Frequent episodes of hypoglycemia: The threshold for differentiating frequent and infrequent was set at 2 hypoglycemic episodes per month. More than two

episodes monthly were classified as frequent and those with less were classified as infrequent.

Type 2 Diabetes Mellitus: Insulin independent Diabetes Mellitus; characterized mostly by delayed onset in middle- and late-adulthood.

Chronic Diabetic patient: Patient suffering from T2DM for more than 1 year.

Physical Activity:

High	>30 minutes of exercise/labor intensive activity for 5 or more days a week.
Moderate	>20 minutes of exercise/labor intensive activity for 3 or more days a week.
Sedentary	<20 minutes of physical work done for less than 3 days a week.

BMI: Body index measured in kg (weight)/ m² (height) used to classify individual as underweight, normal, overweight or obese.

- High BMI- greater than 23
- Normal BMI- between 18-23
- Low BMI- less than 18

Addiction to alcohol: Regular intake of more than 140 mL of alcohol/week for more than 6 months.

RESULTS

A total of 174 patients were enrolled in the study. Table 3 provides the demographic characteristics of the study population.

The prevalence of hypoglycemia was observed at an incidence rate of 92.52% (See Figure 1). Among the risk factors, sedentary lifestyle (86%) was most significantly associated (P-value <0.0001) with patient history of hypoglycemic episodes. Conversely, 97% of the individuals with sedentary lifestyle had experienced hypoglycemic episodes (See Table 4).

A similar direct relation was seen with the biometric factor of weight and height. More than three-fourth of the hypoglycemic patients had a higher BMI of greater than 23 (p-value is <0.0001) (See Table 5). Individuals with persistent or prolonged duration of T2DM had frequent episodes of hypoglycemia (See Table 7).

Treatment induced hypoglycemia was observed in patients on insulin therapy (96.1%) or oral antidiabetic medications (76.5%) (See Table 6).

Diet irregularity and alcohol addiction were not significant risk factors associated with hypoglycemic episodes.

Table 1: Stanford Hypoglycaemia Questionnaire

Symptoms	Never	Once	More than once (Total no. to be mentioned)
Do you have any uneasiness?			
Do you experience unexplained profuse sweating?			
Do you have trembling/shaking?			
Any palpitations?			
Have you experienced any altered movements/seizures?			
Do you have any difficulty in thinking, concentration, speech, and vision?			
Do you have extreme weakness/dizziness/giddiness?			
Any episodes of loss of consciousness?			
Do you experience disturbed sleep/ nightmares?			
Any episodes of early morning headache?			
Any documented low blood glucose values?			

Table 2: Questionnaire for possible hypoglycemic risk factors

S. No	Questions	Responses
1	Patient suffers from which type of diabetes mellitus? Type I Type II	
2	What is the duration for which the patient has suffered from DM? Duration- Short term Long term	
4	What is the BMI of patient? BMI-	

S. No	Questions	Responses
	1-Underweight 2-Normal 3-Overweight 4-Obese	
5	Is the patient addicted to alcohol? 1- Yes 2-No	
6	What is the amount of physical activity being undertaken daily by the patient? 1-High 2-Low 3-Sedentary	
7	What type of diet does the patient intake and is it adequate? Adequate or not: 1-Mixed 2-Vegetarian	

Table 3: Demographic characteristics of the study population

Characteristics	N
Total	174
Gender	
Male	95
Female	79
Religion	
Hindu	124
Islam	49
Education status	
Illiterate	30
Till 5 th grade	17
10 th grade	59
12 th grade	32
Bachelor's degree	29
Postgraduate	6
Marital status	
Married	146
Unmarried	18
Widow	8
Divorcee	1
Dwelling	
Urban	124
Rural	50
Duration of diabetes > 1 year	162
Duration of diabetes ≤1 year	12

Table 4: Prevalence of hypoglycemia according to lifestyle

Hypoglycemia	Sedentary lifestyle	Physically active	Margin row totals
Present	139 (79.88%)	22 (12.6%)	161
Absent	5	8	13
Margin column totals	144	30	174

The Chi-square statistic with Yates correction is 16.116. The p-value is 0.00006.

Table 5: Prevalence of hypoglycemia according to BMI

Hypoglycemia	High BMI	Normal/Low BMI	Margin row totals
Present	126 (72.41%)	35(20.11%)	161
Absent	3	10	13
Margin column totals	129	45	174

The Chi-square statistic with Yates correction is 16.335. The p-value is 0.000053.

Table 6: Association of insulin therapy with hypoglycemia

Hypoglycemia	Insulin	Oral drugs	Margin row totals
Present	148 (85.03%)	13 (7.47%)	161
Absent	9	4	13
Margin column totals	157	17	174

The Chi-square statistic with Yates correction is 4.6892. The p-value is 0.030354.

Table 7: Association of long-term or short-term type 2 diabetes mellitus with hypoglycemia

Hypoglycemia	Long term	Short term	Margin row totals
Present	153 (87.93%)	8 (4.59%)	161
Absent	9	4	13
Margin column totals	162	12	174

The Chi-square statistic with Yates correction is 8.7757. The p-value is 0.003053.

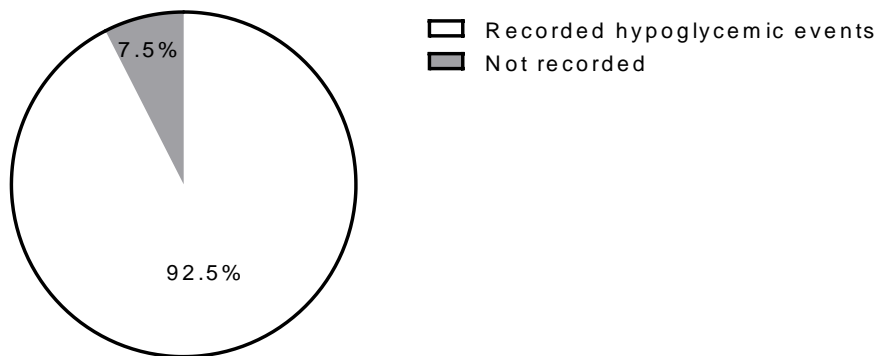


Figure 1: Episodes of hypoglycemia recorded in diabetic patients

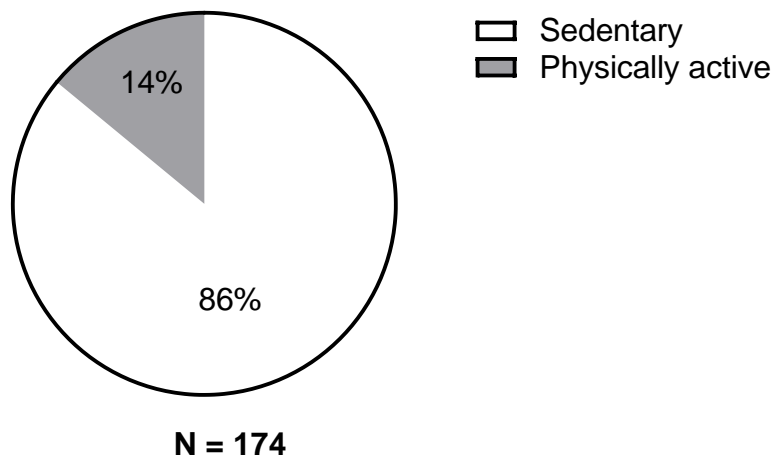


Figure 2: Hypoglycemic individuals with sedentary lifestyle

DISCUSSION

Diabetes is associated with increased incidence of hypoglycemic episodes in majority (92%) of the individuals. Sedentary lifestyle, high BMI, duration of diabetes, type of anti-diabetic therapy were significant factors associated with frequent episodes of hypoglycemia.

Iatrogenic factors are the most common cause of severe hypoglycemic events requiring immediate medical assistance and treatment [7]. In our study, the prevalence of hypoglycemia amongst T2DM patients

was found to be 92.58%. A similar study conducted in southern region of India, reported that the prevalence of hypoglycemia was 57.44%. Severe hypoglycemia was found in 10.7% of the patients [4]. In the 2008 ACCORD trial, it was determined that intensive pharmacotherapy [defined as a goal to achieve hemoglobin A1C (HbA1c) of less than 6.0%] did not significantly reduce any major cardiovascular events and was associated with increased mortality and risk for hypoglycemia [8]. Insulin was identified as major factor causing hypoglycemia even in T2DM patients [9]. These results are likely like the results obtained in our

study which showed prevalence rate of hypoglycemia 94.26% (148 patients) in patients taking insulin as medication (157 patients). These results showed that patients on insulin therapy are at greater risk of frequent hypoglycemic episodes as insulin works directly on plasma glucose and attaining glycemic control in these patients should be accompanied with strict monitoring and effective patient counselling.

Lifestyle modification in terms of exercise and diet is being increasingly accepted as a therapy for prevention and reversal of diabetes in initial state. In the Diabetes Prevention Program (DPP) trial, diet and exercise alone decreased the rate of onset of diabetes mellitus by 58% after 3 years [13]. A lifestyle intervention trial performed in 2019 in pacific islands reported that modification in physical activities and regular diet improved glycemic control [14]. Therefore, obesity often leads to failure of oral hypoglycemics and worsening over insulin. Thus, higher BMI causes higher incidence of hypoglycemic episodes. In our study, 78.26% of the patients who had history of more than one hypoglycemic episode had BMI above 23.

Frequency of hypoglycemia is observed to be directly associated with the chronicity of the disease, the insulin resistance tends to deter as the age increases and disease progresses towards complications. A paper published in 2015 indicated towards increased risk of serious hypoglycemia in older population ($P < 0.05$). Persons aged ≥ 80 years had a higher relative risk of developing hypoglycemia (RR 1.8, 95% CI, 1.4 to 2.3) [15].

Alcohol inhibits only gluconeogenesis in the body, whereas glycogenolysis remains unaltered. Thus, hypoglycemia does not occur immediately after alcohol consumption but may happen later when the glycogen stores are depleted. However, alcohol consumption is not considered as a major risk factor in this study since the location where this study was conducted i.e., Vadodara has outlawed the sale of alcoholic beverages to common citizens, thus making it unlikely that people will consume alcohol and the estimates may not be representative of general population. Other factors that cause hypoglycemia are insulin secreting tumor and chronic hepatic and renal diseases.

CONCLUSION

Increased incidence of hypoglycemia is significantly associated with pharmacological and non-pharmacological factors such as insulin therapy, sedentary lifestyle, obesity, and chronicity of the disease. This knowledge shall help medical practitioners to improve individualized care, planning further course of action for control of diabetes and maintain glycemic control in patients with aim to prevent hypoglycemic crisis and related complications.

Acknowledgments: The authors acknowledge the writing support provided by Tatineni Swathi from Arkus research Pvt. Ltd.

Competing Interests: The authors declare that they have no competing interests related to this manuscript.

Funding Sources: No funding sources were used for the conduct of the study or preparation of this manuscript.

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