ORIGINAL RESEARCH

Incidence of Nocturnal Hypoglycemia in Type II Diabetes Patients with Normal Hba1c, Attending A Teritary Care Medical College Hospital in South India

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ABSTRACT

Background: Diabetes mellitus is a non-communicable disease that has a high prevalence in our country and is known for causing both microvascular and macrovascular complications, especially in patients with uncontrolled HbA1C. Since the beginning of clinical use in the 1970s, hemoglobinA1c (A1c) has become the standard tool for monitoring glycemic control in patients with diabetes. The role of the A1c test was broadened in 2010, when the American Diabetes Association added A1c as a diagnostic criterion for diabetes. Because of hemoglobinA1c's integral role in diagnosis and treatment, it is important to recognize clinical scenarios and interfering factors that yield false results1. HbA1C has been traditionally done in patients with diabetes to assess the previous three months' average glycemic control. But it has got its pitfalls. A patient with hyperglycemic and hypoglycemic episodes can have a normal HbA1C because HbA1c shows just an average value. A normal HbA1c doesn't mean that the patient was in a euglycemic state for the past three months. Both intra-day and inter-day variability in blood glucose levels can contribute significantly to HbA1C levels. Nocturnal hypoglycemia is usually missed because most of the patients are not trained to check for blood sugar values during sleeping hours. Quite often, patients with normal HbA1c are found to have a high incidence of nocturnal hypoglycemia; especially those who are on twice daily premixed insulin. Even with the use of insulin pumps and long-acting insulin analogs, severe hypoglycemia is common in patients with type 1 diabetes, especially during sleep at night. In the Diabetes Control and Complications Trial, more than half of severe hypoglycemic events occurred during sleep (1), and other studies have shown an even greater incidence of severe nocturnal hypoglycemic events in type 1 diabetes (2). Moreover, Sovik and Thordarson (3) reported that among patients aged <40 years who died over 10 years period, 6% of the deaths were due to "dead-in-bed" syndrome, which in many instances probably was the result of severe nocturnal hypoglycemia. Delayed glucose-lowering effects of afternoon exercise (4), sleep-induced defects in counterregulatory hormone responses to hypoglycemia (5–7), and missed bedtime snacks (8) are among the contributing causes of severe nocturnal hypoglycemic events.

Aim: To find the incidence of nocturnal hypoglycemia in type 2 diabetes patients with normal HbA1C levels

Objectives

- To find the incidence of nocturnal hypoglycemias in patients with normal HbA1C (<7%).
- To detect asymptomatic nocturnal hypoglycemias and its contribution to HbA1C in patients who have normal HbA1C.
- To pick up nocturnal phenomena like dawns and the Somogyi phenomenon.

Methods: A total of 100 patients between 18-60 years under both OP and IP care were examined, after excluding patients with known conditions that can falsely elevate or bring down the HbA1C levels like anemia, uremia, severe hypertriglyceridemia, severe hyperbilirubinemia, pregnancy, hemolyticanemia, splenomegaly, and chronic alcoholics. A detailed history of the patient was taken including the treatment history to know the duration of the disease and proper drug compliance. All the patients enrolled in our study were monitored for two weeks by attaching an Abbott Freestyle Libre Pro CGMS device onto the patient's left arm posterior aspect. After the completion of two weeks with CGMS, the sensor was removed from the patient's body and subjected to assessment and processing of AGP (Ambulatory glucose profile).

Results: At least one episode of nocturnal hypoglycemia was detected in 28 patients and 9 of the total 28 patients had prolonged hypoglycemia lasting for more than 2 hours. A higher incidence of nocturnal hypoglycemia was seen among the patients who were on insulin, especially pre-mixed insulin.

Conclusion: A high prevalence (28%) of nocturnal hypoglycemia including asymptomatic hypoglycemias was seen in even patients with normal HbA1C levels and approximately 10% of the total patients had TIR above 95%.
Keywords: Diabetes mellitus, HbA1C, CGMS, Nocturnal hypoglycemia

INTRODUCTION

India is well known as the Diabetic capital of the world with its rapidly escalating prevalence rates rising from less than 3% in 1970 to 7.2% in 2019 with 62 million people suffering from the disease9. The rapid socioeconomic transition and the increased genetic susceptibility of the Indian population along with the unhealthy high-calorie diets and sedentary lifestyle has made the country one of the epicenters of the global DM pandemic10,11.

The term 'diabetes' describes a group of metabolic disorders characterized and identified by the presence of hyperglycemia in the absence of treatment. The heterogeneous aetio-pathology includes defects in insulin secretion, insulin action, or both, and disturbances of carbohydrate, fat, and protein metabolism. Diabetes is classified into two types, with type 2 also called non-insulin-dependent diabetes mellitus primarily caused due to various degrees of β-cell dysfunction and insulin resistance; commonly associated with overweight and obesity12. With diabetes being known as the disease of the vasculature, it leads to both microvascular and macrovascular complications as the disease progresses13,14,15.

Vascular complications of diabetes result from long-lasting unsatisfactory glycemic control. We usually assess glycemic control based on the value of glycatedhemoglobin HbA1c. The glycatedhemoglobin test, however, says nothing about short-term glycemic fluctuations. Recently, continuous monitoring of glycemia has enabled us an in-depth assessment of changes in glucose concentrations, called glycemic variability. In connection with the research into short-term glycemic variability, also the study of long-term fluctuations in glycemic control based on HbA1c variability has now intensified. Glycemic variability may be related to oxidation stress, endothelial dysfunction, and inflammation, the factors traditionally associated with vascular damage. Several studies have described the relationship of glycemic variability to macrovascular complications of diabetes16

It is increasingly recognized that glycemic variability (GV), referring to oscillations in blood glucose levels and representing either short-term or long-term GV, is involved in the pathogenesis of diabetic complications and has emerged as a possible independent risk factor for them16.

While glycatedhemoglobin (HbA1c) is considered the gold standard for determining glycemic management, it has numerous disadvantages, such as a lack of data on glycemic fluctuation or hypoglycemia risk. Moreover, it provides only a single reading, which represents the average of glucose levels over 2–3 months but does not guide change in treatment. Especially, in cases where SMBG readings are discordant with HbA1c, CGM helps identify the actual time when the glucose level is high, low, or within range. Even titration of dosages of medications is possible by studying the trends and day-night glucose patterns of individual patients with diabetes to control fasting or postprandial glucose levels with much more precision. Thus, with the advent of CGM technology in recent years, glycemic control techniques have progressed beyond HbA1c. They incorporate contemporary glucose metric concepts such as glycemic variability (GV) and time-in-range (TIR) glucose. The professional flash glucose monitoring system is one unique CGM device that generates an ambulatory glucose profile (AGP). This AGP is a collated report that represents several days of glucose data in a 24-h model day format, revealing GV, and highlighting areas that require immediate attention. In contrast to attempting mathematical formulas for deriving GV, a demonstration of GV through this tool helps not only in diagnosis and planning of treatment lines for the patient but also as an educational tool to help patients understand their diabetes and thereby take informative actions accordingly. Utilizing AGP obtained via CGM has shown improvement in quality of life by improving glycemic control, and lowering the frequency of hypoglycemia through the increased opportunity of identification of such events With the prevalence of type 2 DM in the adolescents and young adults dramatically increasing, they are in a higher risk for such chronic but often overlooked microvascular and macrovascular complications. Even though HbA1C is routinely assessed, the patients should also be screened for nocturnal glycemic variability to ensure euglycemia around the clock.

A phenomenon known as the dawn phenomenon was introduced by Dr.Schimdt in the 1980s, stating that morning hyperglycemia is due to the decreased levels of endogenous insulin secreted at night. The dawn phenomenon also contributes to morning hyperglycemia to increased concentrations of insulin-antagonist hormones. The dawn phenomenon is comparable to the Somogyi phenomenon, which attributes morning hyperglycemia to counterregulatory hormones from low glucose. The dawn phenomenon has been noted to occur more commonly than the Somogyi phenomenon. While the two theories are not seen in all cases of insulin-dependent diabetics, it is important to note that the

best way to prevent either is optimal diabetes control with the proper insulin therapy.

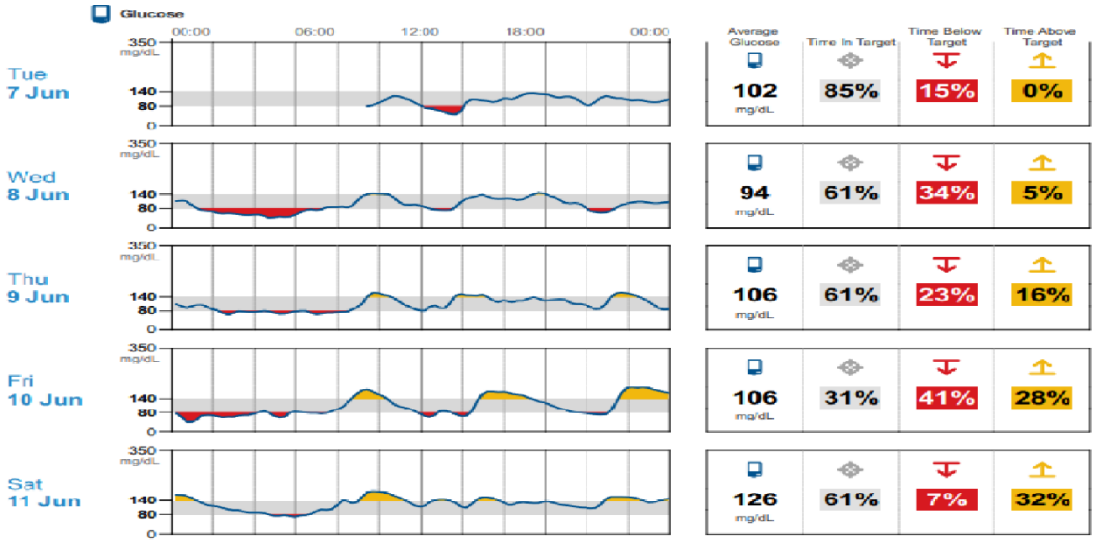
The Somogyi phenomenon states that early morning hyperglycemia occurs due to a rebound effect from late-night hypoglycemia. However, the dawn phenomenon does not include hypoglycemic episodes to be a factor. Somogyi proposed that when blood glucose levels drop too low during the late evening, activation of counterregulatory hormones such as adrenaline, corticosteroids, growth hormone, and glucagon may be observed, leading to activation of gluconeogenesis and resultant hyperglycemia in the early morning.

MATERIALS AND METHODS

STUDY DESIGN

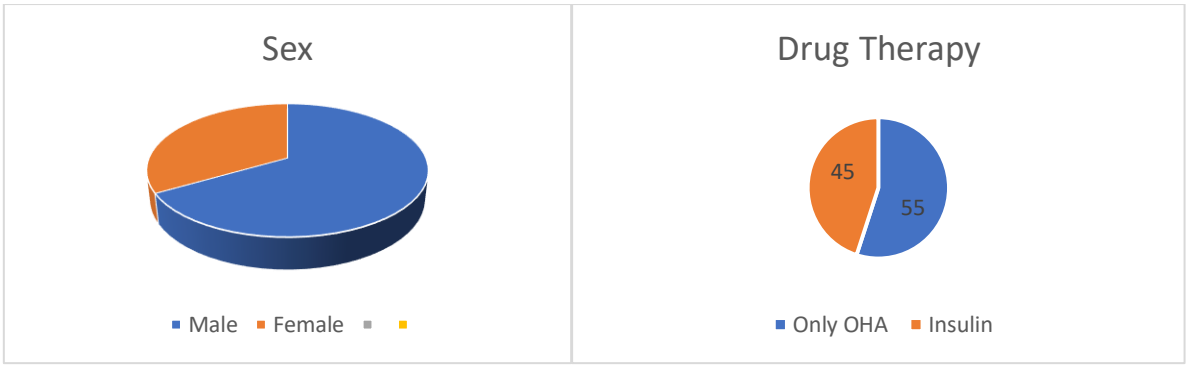
The study was a Descriptive Cross-sectional Study which was conducted on OP patients at the Diabetic Clinic, Department of Internal Medicine. Amala Institute of Medical Sciences, Thrissur, Kerala during the period of August 2020 to July 2022. The patients who were selected for the study were known to have Type 2 Diabetes mellitus according to the ADA22 criteria and were under OPD care with an HbA1C lab value of less than 7%. These patients included all males and females between the ages of 18 – 60 years. Patients with anemia, uremia, severe hypertriglyceridemia, severe hyperbilirubinemia, pregnancy, hemolyticanemia, splenomegaly, and chronic alcoholics were excluded from the study.

The sample size of the study was 100 with 64 males and 36 females participating in the study. A consecutive sampling method was used. Informed consent was obtained from all the participants. A detailed history of the patient was taken including the treatment history (OHAs and insulin), time and the number of hypoglycemic episodes, drug compliance, method of insulin injection, and the duration of diabetes. All the patients enrolled in this study got Abbotts's Freestyle Libre Pro sensor attached to the posterior aspect of the left arm. All the precautions related to the device were conveyed to the patient in detail. After completion of two weeks, the data from the sensor was retrieved and assessed including nocturnal episodes of hypoglycemia, estimated HbA1C, and time in range. Hypoglycemia was documented as an interstitial sugar level of less than 70mg/dL. The lower blood sugar range in the reader device was set at 70mg/dL and the upper range was kept at 140mg/dL. In the graphs, any blood sugar reading below 70mg/dL will be shown as red and any value above 140mg/dL will be shown as yellow. Next to the daily graphs, we will see the average glucose of that particular day, the percentage of the time spent in range, above range, and below range as well. The predicted HbA1c levels as per the 14-day recordings will also be processed.



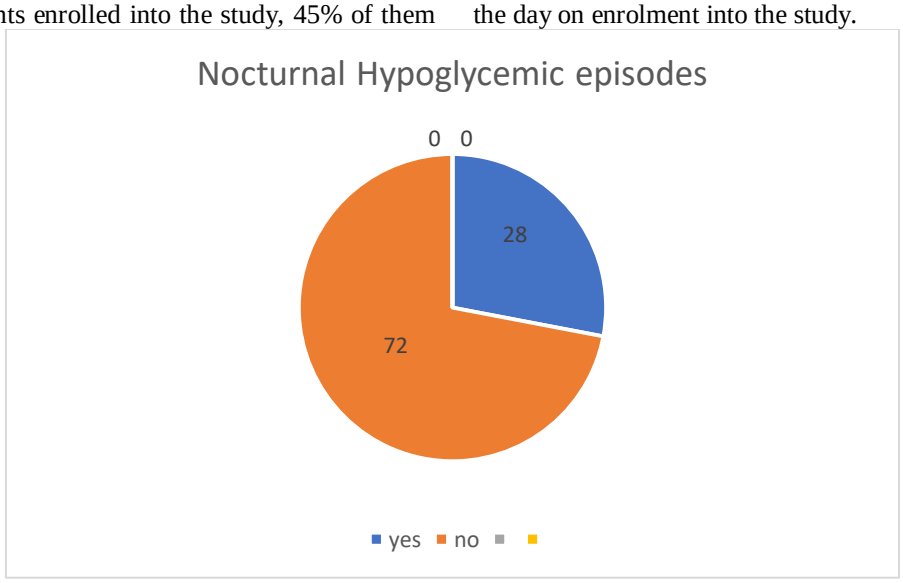
DATA ANALYSIS

The incidence of nocturnal hypoglycemia was calculated from the final report of CGMS. 14 individual 24-hour graphs were obtained during the study period of two weeks. All the glucose readings below 70 was taken as one episode of hypoglycemia. The data obtained was entered in MS Excel worksheet and worksheet analysis was done.

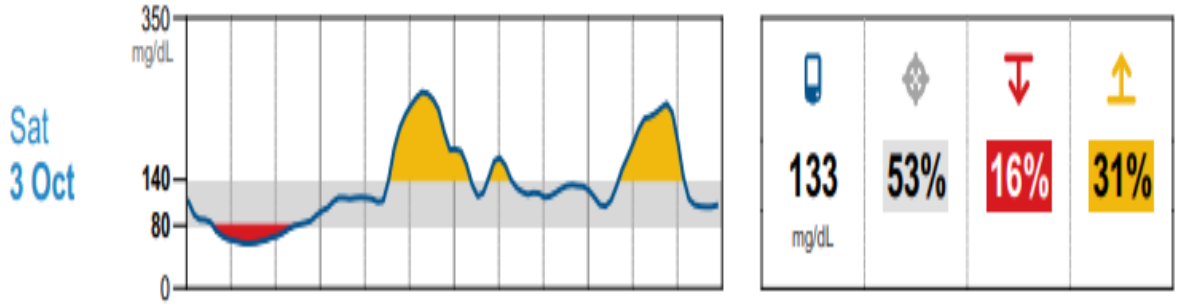


RESULT

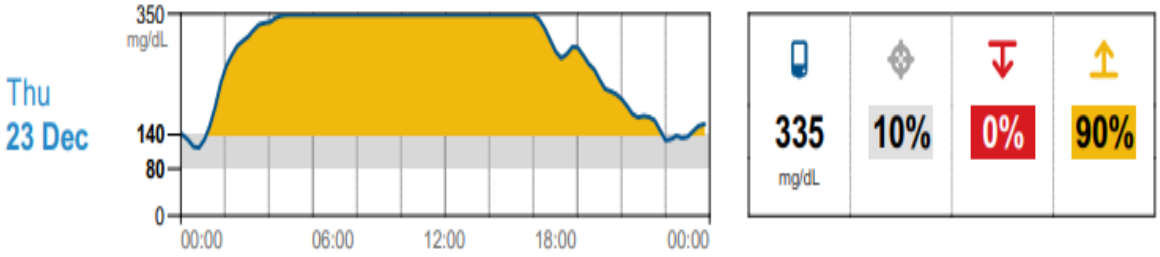
In this study, 100 subjects were evaluated for nocturnal hypoglycemia out of which 64 were males and 36 were females. The mean age of the study population was 50.97 +/- 8.36 (mean +/- SD). Out of the 100 patients enrolled into the study, 45% of them were currently using insulin while the rest 54 patients were on OHAs. 30% were on twice daily pre-mixed insulin while 12% were on basal bolus and 3% were on basal plus insulin regimen. In the study, 80% of the patients had normal fasting blood glucose levels on the day on enrolment into the study.



It was found during the study that 28 out of 100 subjects had nocturnal hypoglycemic episodes and 9% had prolonged hypoglycemia lasting for than 2 hours. Only 50% of the nocturnal hypoglycemic episodes were detected by the patients which means 14% of the total study population had asymptomatic nocturnal hypoglycemias.



Somogyi phenomenon was noted in 3 out of 100 patients enrolled into the study which has been a proposed phenomenon in insulin-dependent diabetic patients. These patient's night insulin dose was reduced in order to avoid nocturnal hypoglycemia.



Dawn phenomenon was detected in 5 patients which required escalation of night dose of insulin.

CONCLUSION

This study evaluated the incidence of nocturnal hypoglycemias in patients with type II diabetes which is very often missed during routine practice. Hypoglycemia in a patient, be it nocturnal or daytime, predisposes them to cardiovascular co-morbidities and mortality. Asymptomatic hypoglycemias even during the daytime may be missed but it may later predispose the patients to autonomic instability and even death. Detection of these hypoglycemic episodes at an earlier stage might help the clinician to slow down the progression of the disease and to aim at better glycemic control. More studies need to be done to understand the pathophysiology and mechanism of those hypoglycemias occurring without insulin or secretagogues, with emphasis on better diagnostic and therapeutic measures. It may not be practical to assess for both daytime and nocturnal hypoglycemias at every routine visit, these assessments can be done yearly or at regular intervals as a part of routine screening similar to diabetic retinopathy and nephropathy. It is high time we enlist this unforeseen complication along with the known complications of the disease such as peripheral neuropathy and retinopathy since hypoglycemic complications heavily contribute to mortality and causes significant morbidity. The nocturnal glycemic excursions are very important as far as a diabetes patient is concerned because the time spent during sleep approximately ranges from 6-8 hours which will amount to 25-33% of the entire day. The study and research in this area of nocturnal hypoglycemic events are still lacking and more research is required for better detection and management of such patients.

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