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ORIGINAL RESEARCH

Correlation Between Hba1c and Time in Range in Type 2 Diabetes Patients with Normal Hba1c, Attending A Tertiary 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, hemoglobin A1c (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 hemoglobin A1c'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 euglycemic state for the past three months. Both intra-day and inter-day variability in blood glucose levels can contribute significantly to HbA1C levels. To address this area, something new has come up with the name "TIME IN RANGE". Time in range is the amount of time you spend in the target blood sugar (blood glucose) range—between 70 and 180 mg/dL for most people. Most people with type 1 and type 2 diabetes should aim for a time in range of at least 70 percent which means patients must aim for roughly 17 out of 24 hours each day to be in range (not high or low).). Some may have different targets. This is usually assessed by using a continuous glucose monitoring device and monitoring the glycemic crests and troughs. From the graphs and other data generated by the CGMS device, it's easy to calculate the time the patient spent "out of the range", both high and low. With more and more insights into this area, HbA1C is being gradually replaced by TIME IN RANGE (TIR). **Objective:** The objective of the study is to find the correlation between HbA1c and "TIME IN RANGE" in patients with normal HbA1C levels. **Methods:** A total of 99 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, hemolytic anemia, splenomegaly, and chronic alcoholics. The 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 Abbott Free style 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). An AGP report is a standardized, single-page report that includes glucose statistics like TIR, a summary glucose profile, and daily glucose graphs. It converts blood glucose readings from a CGM device into a detailed picture, allowing you to quickly visualize the time you spend above and below your target range. The report is based on 14 days of CGM data.

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RESULTS: The TIR >70% was found only in 62 patients and only 9 of the total patients had TIR >95%. A higher incidence of glycemic variability was seen among the patients who were on insulin. 28% of the patient population had nocturnal hypoglycemias too. **Conclusion:** A very high prevalence of glycemic variability including asymptomatic hypoglycemias was seen in even patients with normal HbA1C levels and approximately 10% of the total patients had TIR above 95%.

Key words: Diabetes mellitus, HbA1C, CGMS, Time in Range, Ambulatory Glucose Profile.

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 disease[2]. The rapid socioeconomic transition and the increased genetic susceptibility of the Indian population along with the unhealthy high-calorie diets and sedentary lifestyle have made the country one of the epicenters of the global DM pandemic[3,4].

The term 'diabetes' describes a group of metabolic disorders characterized and identified by the presence of hyperglycaemia 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, type 1 and type II of which type II is also called non-insulin-dependent diabetes mellitus primarily caused by various degrees of β-cell dysfunction and insulin resistance; commonly associated with overweight and obesity[5]. Diabetes being known as the disease of the vasculature, leads to both microvascular and macrovascular complications as the disease progresses[6,7,8].

Vascular complications of diabetes result from long lasting unsatisfactory glycemic control. We usually assess glycemic control based on the value of glycated hemoglobin HbA1c. The glycated hemoglobin 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 relation of glycemic variability to macrovascular complications of diabetes[9]

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 them[20.]

While glycated hemoglobin (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 ATTD consensus panel - should strive to spend more than 70% of their waking hours (about >17 h) in TIR (70–180 mg/dL), with TBR (70 mg/dL) less than 4% and TAR (>180 mg/dL) <25%

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 as a 24-hour 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 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 TIR which is a better single predictive factor for euglycemia is often understated and needs to be given equal relevance.

OBJECTIVES

- To find the correlation between HbA1c and Time in Range in patients with normal HbA1C (<7%).

To detect asymptomatic hypoglycemias and hyperglycemias and its contribution to HbA1C in patients who have normal HbA1C.

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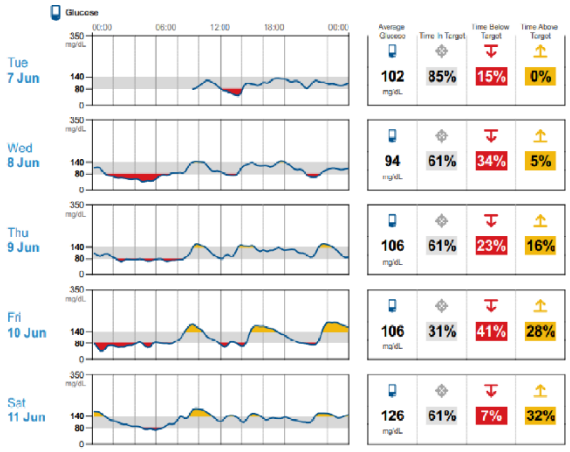
MATERIALS AND METHODS

Study Design

The study was a Descriptive Cross-sectional Study which was conducted at the Department of Internal Medicine (OP Patients and IP patients). 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, who were under OPD care or IP care, with HbA1C lab value 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, hemolytic anemia, splenomegaly, and chronic alcoholics were excluded from the study. The sample size of the study was 99 with 51 males and 48 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 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. After completion of two weeks, the data from the sensor was retrieved and assessed including estimated HbA1C, percentage of time above and below the target, TIR, and other parameters.

Calculation Of Time in Range

The data retrieved from the CGMS after the completion of two weeks of study was analysed. The daily glycemic fluctuations are displayed as fourteen separate graphs (2 weeks). The percentage of time in range on a daily basis as well as 2 weeks, is processed and the data is taken for the study purpose.

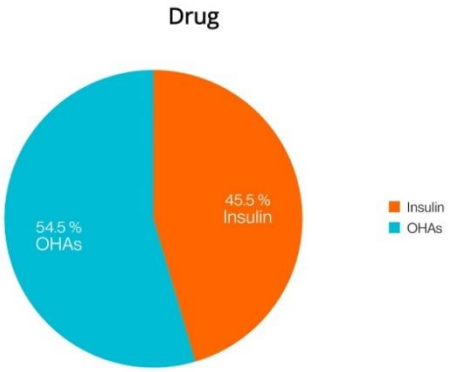


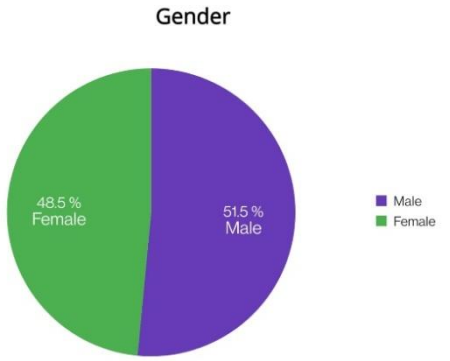
Data Analysis

The data obtained was entered in MS Excel worksheet and worksheet analysis was done using the SPSS software version 23. The correlation between the patient's HbA1C value and the estimated HbA1C value from the CGMS report including TIR was calculated using the Pearson correlation test. The association between the patient's HbA1C and percentage of TIR was calculated using the chi-square test with $p < 0.05$ considered to be significant

RESULT

In this study, 99 subjects were evaluated for TIR out of which 51 (51.51 %) were males and 48 (48.49 %) were females. The mean age of the study population was 50.97 +/- 8.36 (mean +/- SD). Out of the 99 diabetic patients, 45 (45.45 %) of them were currently using insulin while the rest 54 (54.5%) patients were on OHAs.





It was found during the study that only 62 out of 99 subjects had time in the range above 70%. It was strange to note that just 9 patients (<10%) out of 99 study subjects had TIR above 95%, which means that by including TIR assessment in the routine clinical practice, we can improve the time spent by the patients in euglycemia considerably. The reason for the glycemic variability may be obtained primarily from the patient's diet patterns and drug therapy.

The correlation between patients' baseline HbA1C from the lab and the estimated HbA1C after completion of the CGMS was assessed in these 99 subjects.

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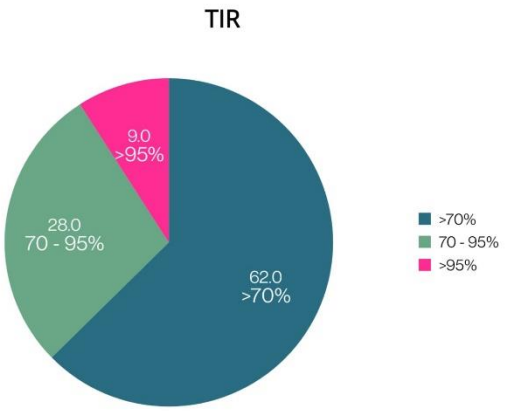

DISCUSSION

The purpose of diabetes treatment is to maintain good glycemic control from the early stage of diabetes and to prevent the onset and progression of complications (HbA1c) has been used as a golden standard index of glycemic control. HbA1c is the most commonly used method for evaluating blood glucose control in clinical treatment and is recognized as the key surrogate marker for the development of diabetic complications. High GV is associated with the development and progression of diabetic vascular complications, the exacerbation of hypoglycemic risk, and the deterioration of patient quality of life (QOL)

This AGP is a collated report that represents several days of glucose data as a 24-h model day format, revealing GV, and highlighting areas which 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 line 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.

There are relatively few data on the TIR targets that have been achieved in patients with T2DM. Beck *et al*. revealed in the multiple daily injections and continuous glucose monitoring in diabetes (DIAMOND) study that 158 T2DM patients receiving Multiple daily Insulin Injections (MDI) increased their TIR from 55.6% to 61.3% after 24 weeks of CGM use.[21] In 2019, Vigersky and McMahon published a meta-analysis indicating that a 10% change in TIR resulted in a 0.8% reduction in HbA1c. Another study is by Lu *et al*. who published a cross-sectional study assessing the correlation between TIR and albuminuria. Also we have studies of retinopathy and TIR as well.

The DCCT established a strong correlation between HbA1c levels and the risk of diabetes-related chronic vascular complications. Beck *et al*. examined the association between TIR and the development and/or progression of microalbuminuria and diabetic retinopathy using the DCCT trial dataset. He showed that for every 10%-point decrease in TIR, the risk of developing microalbuminuria increased by 40%.

While TIR has been seen as beneficial across types and stages of diabetes, there are select patient profiles that may benefit from adopting this metric to achieve optimal glycemic control.

1. Oral anti-diabetic (OAD) inadequacy – This includes patients who have been on maximized doses of OADs agents for quite some time and yet uncontrolled, leaving them insulin as the last resort. Sometimes, even though OADs are not maximized, patients may be afraid of insulins and would wish to delay the initiation as much as possible.
2. Hypoglycemia in patients on insulin – In India, premixed insulin dominates insulin usage for diabetes management. The popularity of premixed insulins predisposes the patients to hypoglycemia. A large proportion of patients develop hypoglycemia unawareness by the time they reach 10–15 years of diabetes and hence, hypoglycemia remains undiagnosed
3. Gestational DM – Pregnancy is a metabolic stress for the human body and with diabetes poses an array of challenges for the hormones to cause huge degree of glucose fluctuations to meet the increased metabolic demands. At the same time, the pregnancy outcome is always very crucial for the parents; hence, tight glucose control becomes vital both before and especially during pregnancy
4. Diet and lifestyle management for glucose control – Diet and lifestyle modification are inevitable in all forms of diabetes management. However, some patients find it easy, while some difficult to adopt changes suggested by their diabetes educator/counselor or physician/diabetologist/endocrinologist. Enabling to visualize the impact of dietary and lifestyle changes by using CGM and TIR, it will help empower and motivate the patients to manage diabetes on their own.

Pre and post-hospitalization – Patients with diabetes have to deal with hospitalization quite often. Good glucose control is critical to ensure faster recovery of patients. In medical causes for admission, glucose

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control may decide the number of days in hospital-based recovery; whereas in surgical cases, glucose control determines the decision to proceed with the surgery and for better postsurgical outcomes.

CONCLUSION

This study evaluated the incidence of high glycemic variability in patients with normal HbA1C. 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 and low TIR 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 and TIR assessments at every routine visit, these assessments can be done yearly or at regular intervals as a part of routine screening like 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 the mortality and cause significant morbidity. The studies and research in this area of nocturnal hypoglycemic events and TIR are still lacking, and more research is required for better detection and management of such patients.

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