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Research Article

Correlation between Glycosylated Hemoglobin and Glycemic Variability in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Background & Objectives: Glycosylated hemoglobin (HbA1c) is commonly used to diagnose and monitor diabetes. Still, it has some drawbacks, such as being affected by blood disorders and failing to show changes in blood sugar levels throughout the day. This study examined how HbA1c relates to measures of blood sugar variability, with particular focus on Time in Range (TIR).

Methods: We conducted a cross-sectional study of 70 patients with type 2 diabetes. We collected their HbA1c levels and data from continuous glucose monitoring (CGM). Using the ambulatory glucose profile, we measured glycemic variability, including TIR, time below range (TBR), time above range (TAR), and mean amplitude of glycemic excursions (MAGE). We then analyzed the relationship between HbA1c and these CGM metrics.

Results: HbA1c was strongly linked to TIR ($r = -0.88$, $p < 0.001$) and TBR ($r = -0.29$, $p < 0.01$), and also showed a strong positive link with TAR ($r = 0.91$, $p < 0.001$) and MAGE ($r = 0.85$, $p < 0.001$). Even though some patients had HbA1c below 7.5%, only 55.5% had TIR above 70%. Also, 60% had TBR above 4%, indicating many were at risk of low blood sugar.

Interpretation & Conclusions: While HbA1c remains helpful for assessing overall blood sugar control, it does not reflect changes in blood sugar throughout the day. CGM metrics, especially TIR, give a fuller picture and should be used regularly in diabetes care.

Keywords: Mean amplitude of glycemic excursions (MAGE), Time in range, Continous Glucose monitoring, Blood glucose self-monitoring

INTRODUCTION

Diabetes mellitus is a major metabolic disorder affecting nearly 10% of the global population and about one-fifth of individuals over 45 years, contributing significantly to morbidity and mortality [1]. Glycosylated hemoglobin (HbA1c), as endorsed by the American Diabetes Association (ADA), remains a key diagnostic and prognostic marker, reflecting average glycemic control over 2–3 months [2,3]. According to ADA 2023, an HbA1c target of <7% is appropriate for most non-pregnant adults without significant hypoglycemia, though continuous glucose monitoring (CGM) is required to adequately detect hypoglycemic events.

However, HbA1c has notable limitations. It is influenced by genetic and hematological factors affecting red blood cell turnover and does not capture intra-day or inter-day glucose fluctuations [4,5]. Glycemic variability, encompassing both hypo- and hyperglycemic excursions, is increased in diabetes and contributes to oxidative stress and free radical generation, promoting cardiovascular complications [6,7]. Mean Amplitude of Glycemic Excursions (MAGE) is an important marker of such variability, which has been linked to both microvascular and macrovascular complications [6].

These limitations highlight the need for CGM, considered a "beyond HbA1c" tool [5]. CGM provides detailed metrics, including Time in Range (TIR), Time Below Range (TBR), Time Above Range (TAR), and mean glucose levels. TIR reflects the percentage of time glucose remains within the target range of 70–180 mg/dL, as per ADA guidelines [8]. Higher TIR indicates more stable glycemic control with fewer excursions, thereby reducing complication risk. This study evaluates the correlation between HbA1c and glycemic variability parameters, emphasizing the clinical importance of TIR as a superior marker in diabetes management.

MATERIALS AND METHODS

We conducted this cross-sectional study of stable patients aged 18 to 65 with type 2 diabetes. We did not include patients with end-stage liver or kidney disease, cancer, or those who were pregnant. Seventy patients who agreed to take part were enrolled.

We measured HbA1c using high-performance liquid chromatography. For continuous glucose monitoring, we used the FreeStyle Libre Pro system, which checks glucose levels every 15 minutes for up to 14 days. This system generates an Ambulatory

Glucose Profile[9] that displays key metrics such as TIR, TBR, TAR, MAGE, average glucose, and glucose trends.

Data were entered into Microsoft Excel and analyzed using GraphPad Prism 9.4.1. Correlation between HbA1c and CGM-derived metrics was assessed. We entered the data into Microsoft Excel and analyzed it with GraphPad Prism 9.4.1. We used statistical tests to examine the relationship between HbA1c and CGM metrics. A *p-value* below 0.05 was considered significant.

Ethical Considerations

The study was conducted in accordance with ethical principles and approved by the Institutional Ethics Committee. Written informed consent was obtained from all participants before enrollment. Patient confidentiality was strictly maintained throughout the study.

RESULTS

Continuous glucose monitoring of each of the 70 patients had been done for 14 days using FreeStyle Libre Pro, a CGM device. Figure 1 shows HbA1c and various CGM-related metrics like TIR, TAR, TBR, average blood glucose and MAGE. Besides providing information about the mean glucose concentration, these CGM profiles provided additional details on the patterns of glycemic excursions, as well as potentially dangerous high or low glucose concentrations.

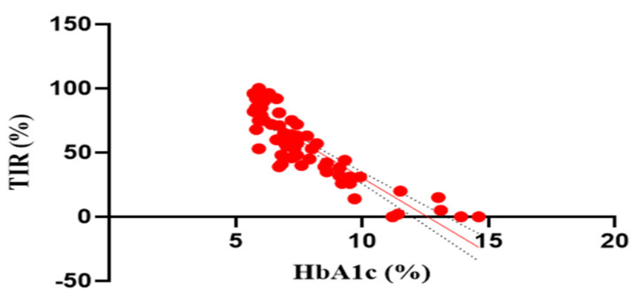
A univariate linear regression analysis has been performed to find out the correlation between HbA1c and glycemic variability-associated parameters (CGM-related metrics). As shown in Figure 1, we observed a strong negative correlation between TIR% and HbA1c% (r value = -0.88, *p-value* <0.001).

From Figure 1, TIR = (-11.71 x HbA1c) + 147.3 showed the correlation between TIR% and HbA1c%. HbA1c values corresponding to TIR of 50, 60, 70, 80, 90, and 100% are calculated and shown in Table 1.

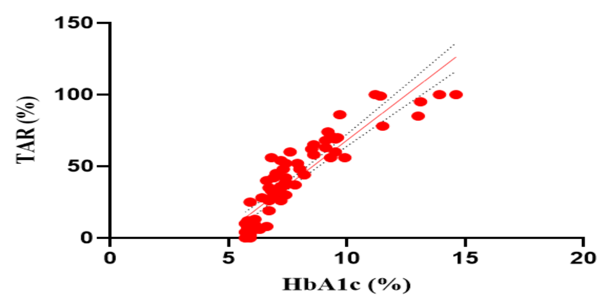
Table 1: Showing values of HbA1c % which correspond to respective TIR using the relation obtained in Figure 1 TIR = (-11.71 x HbA1c) + 147.3

TIR %	*HbA1c %*
50	8.3
60	7.5
70	6.6
80	5.7
90	4.9
100	4.0

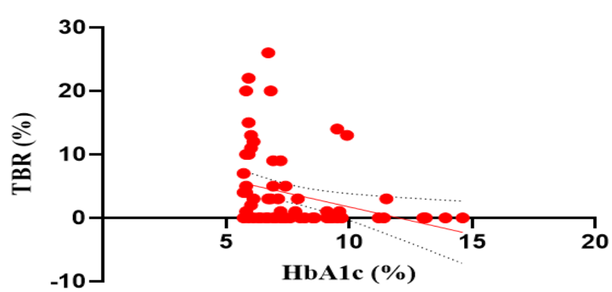
HbA1c, glycosylated hemoglobin; TIR, time in range



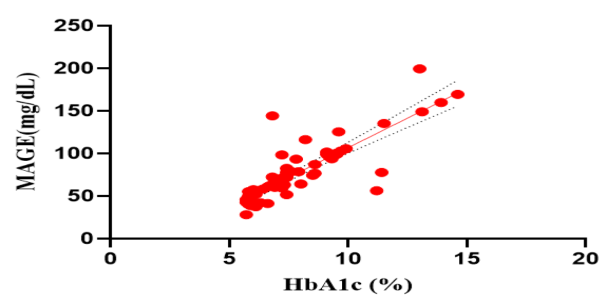
(a) Scatter plot showing the relationship between TIR % and HbA1c %.
r = -0.88, p <0.001



(b) Scatter plot showing the relationship between TAR % and HbA1c %
r =-0.91, p <0.001.



(c) Scatter plot showing the relationship between TBR % and HbA1c %.
r = - 0.29, p <0.01



(d) Scatter plot showing the relationship between MAGE in mg/dL and HbA1c %.
r = 0.85, p <0.001

CGM, continuous glucose monitoring; HbA1c, glycosylated hemoglobin; TIR, time in range; TAR, time above range; TBR, time below range; MAGE, mean amplitude of glycemic excursion

Figure 1: Relationship between different CGM metrics and HbA1c

Table 2: Showing values of HbA1c % which correspond to respective TAR using the relation obtained in Figure 1 TAR = (12.57 x HbA1c) - 57.41

TAR %	*HbA1c %*
5	5.0
10	5.4
15	5.8
20	6.2
25	6.6
30	7.0

HbA1c, glycosylated hemoglobin; TAR, time above range

Table 3: Comparing CGM related metrics of Patient ID 36 and Patient ID 49

	Patient ID 36	*Patient ID 49*
HbA1c %	6.7	6.7
TIR %	81	39
TAR %	19	35
TBR %	0	26

CGM, continuous glucose monitoring; HbA1c, glycosylated hemoglobin; TIR, time in range; TAR, time above range; TBR, time below range; MAGE, mean amplitude of glycemic excursion

Next, we observed a significant positive relation between TAR % and HbA1c % as illustrated in Figure 1 (r value=0.91, *p-value* <0.001).

From Figure 1, TAR = (12.57 x HbA1c) - 57.41 showed the correlation between TAR% and HbA1c %. HbA1c values corresponding to TAR of 5%, 10%, 15%, 20%, 25% and 30% are calculated and shown in Table 2.

Then, we compared Patient Id 36 and Patient Id 49 on the basis of HbA1c and continuous glucose monitoring-related metrics like TIR%, TAR% and TBR%. Figure 2 shows the Ambulatory glucose profile of Patient ID 36 and Patient ID 49. From Table 3, it was evident that Patient ID 36 had better glycemic control as compared to Patient ID 49, despite having an HbA1c of 6.7 in both cases.

We made a comparison with respect to TBR, TIR and TAR between patients with HbA1c less than 6.5% and patients with HbA1c less than 7.5%. This is illustrated in Table 4.

DISCUSSION

Advanced technologies and treatments for diabetes (ATTD) recognize CGM-derived metrics time in range (TIR), Time Above Range (TAR), and Time Below Range (TBR)—as key indicators of glycemic variability with potential to transform diabetes management through personalized therapy [10]. At the ATTD Congress 2019, recommended targets for individuals with type 1 and type 2 diabetes included TIR >70% (70–180 mg/dL), TBR <4% (<70 mg/dL), and TAR <25% (>180 mg/dL).

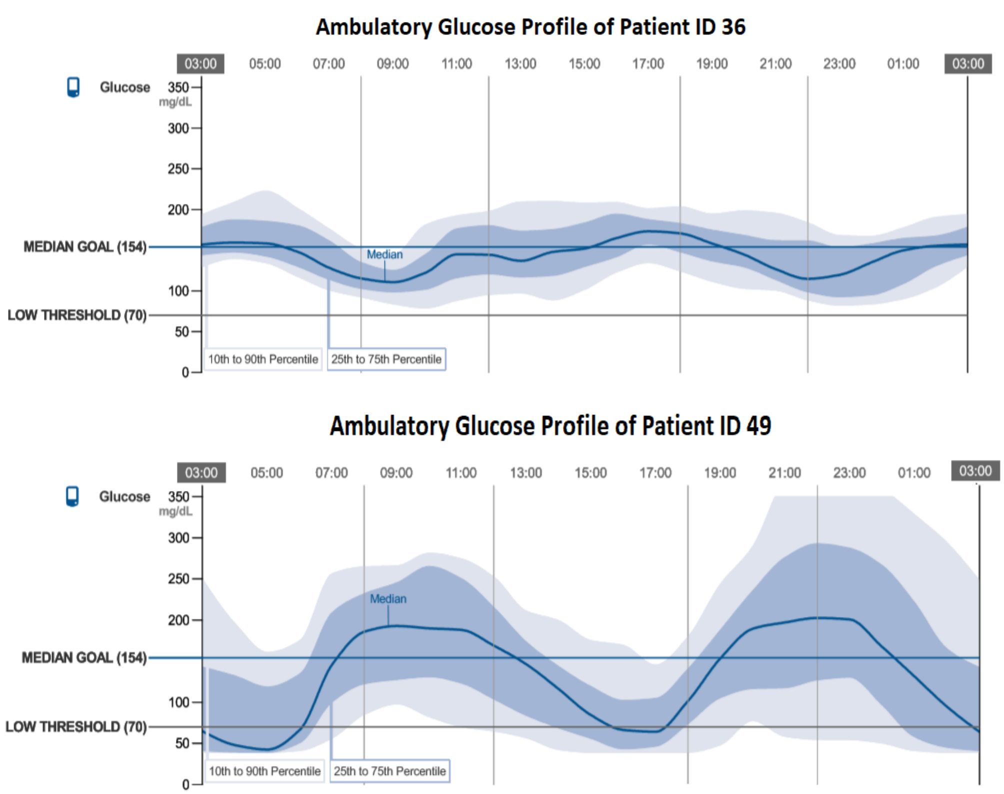


Figure 2: Comparing the Ambulatory Glucose Profile of Patient ID 36 and Patient ID 49.

Table 4: Showing the total number of patients with HbA1c% less than 6.5% and 7.5% and associated CGM metrics findings

	HbA1c less than 6.5	*HbA1c less than 7.5*
Total number of patients	22	45
Total number/ percentage of patients with TBR less than 4%	10 (45.5%)	27 (60%)
Total number/ percentage of patients with TBR more than 4%	12 (54.5%)	18 (40%)
Total number/ percentage of patients with TIR greater than 70%	20 (90.9%)	25 (55.5%)
Total number/ percentage of patients with TIR less than 70%	2 (9.1%)	20 (45.5%)
Total number/ percentage of patients with TAR less than 25%	20 (90.9%)	22 (48.9%)
Total number/ percentage of patients with TAR less than 25%	2 (9.1%)	23 (51.1%)

HbA1c, glycosylated hemoglobin; CGM, continuous glucose monitoring; TBR, time below range; TIR, time in range; TAR, time above range

In our study, HbA1c showed a strong inverse correlation with TIR ($r = -0.88$, $p < 0.001$), with a TIR of 70% corresponding to an HbA1c of ~6.6% (Table I), slightly lower than previous reports of ~6.7–7%11. We also observed that a 1% reduction in HbA1c corresponded to a 12% increase in TIR, compared to 17% reported earlier [11]. HbA1c correlated strongly with TAR ($r = 0.91$, $p < 0.001$), where TAR of 25% aligned with HbA1c ~6.6%, whereas correlation with TBR was weak ($r = -0.293$, $p = 0.014$), indicating limited utility of HbA1c in predicting hypoglycemia. Prior studies similarly report modest correlations of HbA1c with TIR and hyperglycemia, and a negative association with hypoglycemia [12-14].

Historically, diabetes management emphasized strict HbA1c reduction ("the lower, the better"), supported by the UKPDS16. However, later trials such as ACCORD and ADVANCE showed increased mortality or no cardiovascular benefit with intensive targets (<6–6.5%), with the lowest risk observed around HbA1c ~7.5% [15,16]. Despite acceptable HbA1c levels, many patients fail to achieve TIR >70% (Table IV), highlighting glycemic variability undetected by HbA1c alone. Such variability, measurable only by CGM, is linked to oxidative stress and increased microvascular and macrovascular complications [7].

Our study further showed that stringent HbA1c control (<6.5%) was associated with hypoglycemia risk in ~50% of patients, even when TIR targets were met, consistent with findings from ACCORD and ADVANCE. CGM enables the identification and prevention of such events. Mean Amplitude of Glycemic Excursions (MAGE), another marker of variability, showed strong positive correlation with HbA1c ($r = 0.847$, $p < 0.001$), consistent with prior studies [17]. MAGE values >40 mg/dL are associated with higher complication risk [6]. However, variability in MAGE at similar HbA1c levels suggests inter-individual differences, indicating the need for refinement in its calculation as proposed by Marling *et al.* [18].

CONCLUSION

In the management of diabetes, HbA1c plays a crucial role in monitoring and guiding treatment. However, with the advancement and feasibility of the technology, CGM will now add on for further better control and treatment of diabetes as we can see the glycemic trend from intra-day to inter-day variability and hence could modify our treatment more strategically and efficiently with the least chances of hypoglycemia. Finally, the treatment of individual patients could be tailored and long-term complications could be prevented by keeping the patient's blood sugar level within the target range.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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