

## CORRELATION BETWEEN 1,5-ANHYDROGLUCITOL LEVELS AND GLYCEMIC VARIABILITY IN TYPE 2 DIABETIC PATIENTS USING CONTINUOUS GLUCOSE MONITORING

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### ABSTRACT

**Background:** The evaluation and control of glycemic variability (GV) has been one of diabetes treatment targets recently. 1,5-anhydroglucitol (1,5-AG) is a test that can be used to evaluate GV. **Objectives:** 1. To survey the short-term change of 1,5-AG and HbA1c in patients with type 2 diabetes. 2. To assess the correlation between 1,5-AG and GV in patients with type 2 diabetes using continuous glucose monitoring system (CGM). **Subjects and Methods:** A descriptive cross-sectional study was conducted on 38 patients with type 2 diabetes using a CGM system for 7 days at Cho Ray Hospital. Spearman's rank correlation coefficient was used to determine the correlation between two variables. Non parametric tests were used to find the difference between groups at two time points. **Results:** The concentration of 1,5-AG after 7 days from the beginning of using the CGM system during inpatient treatment was 5.98 (5.39-7.01)  $\mu\text{g/mL}$ , greater than the initial time of 2.91 (2.41 - 4.32)  $\mu\text{g/mL}$ ,  $p < 0.001$ . HbA1c levels after 7 days were similar to the measurements at the beginning of the study,  $9.12 \pm 1.92\%$  and  $9.23 \pm 2.07\%$ , respectively,  $p = 0.08$ . There was an inverse, moderate, and statistically significant relationship between the concentration of 1,5-AG and CoV of glycemia in

7 days,  $r$  was  $-0.45$ ,  $p < 0.05$ . **Conclusions:** 1,5-AG can be utilized in evaluating glycemic variability and glycemic control in the short term.

**Keywords:** Diabetes mellitus, 1,5-anhydroglucitol, HbA1c, glycemic variability

### I. BACKGROUND:

Diabetes mellitus is one of the most common metabolic disorders and it is an increasingly global trend. In Vietnam, there are approximately 7 million people with diabetes and diabetes is in the top 7 causes of death. Control of GV is one of the goals of diabetes treatment besides blood glucose and HbA1c level to reduce complications and improve patient's prognoses.

Chronic hyperglycemia is the main risk factor leading to complications in diabetes. However, it is believed that frequent or large fluctuations in blood glucose level can independently contribute to complications associated with diabetes, as well as hypoglycemic events, which are thought to cause increased cardiovascular events in diabetes.

A continuous glucose monitoring system (CGM) can collect data automatically every 5 minutes, helping patients and their physicians more closely monitor their blood glucose levels. This system has been approved by the FDA for the control of day and night blood glucose levels [2].

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**Date of receipt:** 25/9/2023

**Date of scientific judgment:** 30/10/2023

**Reviewed date:** 6/11/2023

Some studies that have looked at the degree of correlation between different methods of GV assessment have demonstrated that the most widely used methods are closely correlated with each other and with previously developed measures. Although standard deviation (SD) is widely used, it has limitation that its use implies measurements of blood glucose follow a normal distribution, which is often not the case in this circumstance.

The methods used to evaluate GV show an important issue since all methods show that GV is significantly affected by average blood glucose: higher average blood glucose levels are associated with higher GV values unless they are calibrated for average blood glucose. Calibrating the average blood glucose of any relationship between GV and a given result is important because a high correlation between GV and mean blood glucose has been demonstrated.

For the reasons mentioned above, the coefficient of variation (CoV) has been proposed as the preferred measure of GV. CoV in CGM is significantly associated with the presence of autonomic neuropathy and cardiovascular pathology in patients with poorly controlled type 2 diabetes.

Time in range (TIR) is the percentage of time in which a patient's blood glucose levels are within the target threshold for a specific period of time. If a diabetic patient has a TIR of 50%, it means that the patient has blood glucose levels within the target threshold for 12 hours per day. Each person's glycemic target threshold may vary. However, most official recommendations set a target threshold of 70 mg/dL to 180 mg/dL (3.9 – 10 mmol/L).

In addition to the mentioned metrics, 1,5-AG may have clinical applications for diabetes diagnosis, evaluation of GV and prediction of diabetic complications. Studies around the world have shown that 1,5-AG has a significant correlation with all GV parameters from CGM. This study was conducted on patients with type 2 diabetes using the CGM system at Cho Ray hospital to evaluate the applicability of the 1,5-AG test in GV monitoring.

**Objective:** 1. To survey the short-term change of 1,5-AG and HbA1c in patients with type 2 diabetes; 2. To determine the correlation between 1,5-AG levels and GV within 7 days in patients with type 2 diabetes using CGM.

## II. SUBJECTS AND METHODS:

### 2.1. Subjects of study:

**Selection criteria:** Type 2 diabetes adult patients ( $\geq 18$  years old) who had been receiving treatment for more than 7 days at the Endocrinology Department of Cho Ray Hospital using the CGM system

**- Exclusion criteria:**

- Severe patients, at risk of death (from severe metabolic acidosis, liver failure, renal failure, respiratory failure, and cardiovascular disease)
- Pregnant women
- Patients with indications for surgery
- Patients with acute complications of diabetes: Coma due to ketoacidosis, coma due to increased osmotic pressure, hypoglycemia
- Patients with  $eGFR \leq 30\text{mL}/\text{min}/1.73\text{m}^2$
- Patients who did not agree to participate in the study

**2.2. Study design:** cross-sectional study.

**2.3. Sample size:** The resulting variable is the value of 1,5-AG, which is a quantitative continuous variable.

$$n = 3 + \frac{4C(\alpha, \beta)}{\left[\ln\left(\frac{1+r}{1-r}\right)\right]^2}$$

In this study, choose  $\alpha = 0.05$  and  $\beta = 0.20$ , then  $C = 7.85$ .

Based on the study [6], there was a correlation coefficient  $r = -0.472$ , using the following formula to calculate:

$$n = 3 + \frac{4C(\alpha, \beta)}{\left[\ln\left(\frac{1+r}{1-r}\right)\right]^2} = 3 + \frac{4 \times 7.85}{\left[\ln\left(\frac{1-0.472}{1+0.472}\right)\right]^2} = 32.87$$

Select  $n = 33$

**2.4. Time and Place of study:** From February to June 2022 at Endocrinology Department and Biochemistry Department – Cho Ray Hospital.

**2.5. Methods of collecting data:**

- Age, gender, results from liver and kidney function tests and dyslipidemia were collected from the patient's medical record.

- 1,5-AG, HbA1c tests were performed at twice: at the beginning of the use of the CGM system (T0) and 7 days from the beginning of using the system (T7d).

- Mean blood glucose (MG), time in range (TIR), coefficient of variation (CoV) in the CGM FreeStyle Abbott system were collected at 7 days from the beginning of using the system (T7d).

**Quantifying 1,5-anhydroglucitol:** The 1,5-AG test was performed on the Siemens Advia 1800 automated biochemical analyzer using enzymatic kinetic measurements and Glycomark reagents. Internal checks with two levels of controls were performed at the same time when running the study sample. A standardized 3500 rpm post-centrifugal for

10 minutes serum or plasma sample without hemolysis was used to perform the test.

**2.6. Data processing and analysis:** The statistical data was analyzed by Stata version 14.0. For quantitative variables, if data followed normal distribution, it would be expressed in mean and standard deviation ( $M \pm SD$ ). If there was an abnormal distribution, the median and interquartile range (Median (IQR)) would be used. Qualitative variables were represented by the ratio (%). The t test was used to compare 2 groups if the data were normally distributed or Wilcoxon test if the data were abnormally distributed. Spearman's rank correlation coefficient was used to determine the correlation between the dependent and independent variable. The difference was considered statistically significant when  $p < 0.05$ .

**2.7. Medical ethics:** This study had been approved by the Ethics Council for Biomedical Research at the University of Medicine and Pharmacy at Ho Chi Minh City according to Decision No. 195/HĐĐĐ-ĐHYD dated February 21, 2022.

### III. RESULTS:

#### 3.1. General characteristics:

During this study, we collected data from 38 type 2 diabetes patients who used the CGM system.

The percentages of the number of men and women was 47.4%. The average age was  $54.9 \pm 16.6$  years. The average age of men and women was  $54.8 \pm 17.1$  and  $55.1 \pm 16.6$  years. The difference between the two group was not statistically significant,  $p = 0.96$ . The age of the youngest is 19 years old and the oldest is 82 years old (Table 1).

**Table 1: Age and gender characteristics of patients with type 2 diabetes using CGM system**

<b>N = 38</b>	<b>Male</b>	<b>Female</b>	<b>P</b>
<b>Gender N (%)</b>	18 (47.4)	20 (52.6)	
<b>Age M ± SD</b>	54.8 ± 17.1	55.1 ± 16.6	0.96*
	54.9 ± 16.6		

\*: t-test

**3.2. Biochemical test results:****Table 2: Biochemical test results of patients with type 2 diabetes using CGM system**

<b>Test</b>	<b>Results</b>	
	<b>M ± SD</b>	<b>Median (IQR)</b>
<b>AST (U/L)</b>	32.5 ± 8.6	32 (27 - 41)
<b>ALT (U/L)</b>	34.1 ± 9.1	34 (22 - 50)
<b>Triglycerides (mg/dL)</b>	108.0 ± 45.2	110 (82 - 122)
<b>Cholesterol (mg/dL)</b>	172.0 ± 16.7	178.0 (146 - 198)
<b>LDL-Cholesterol (mg/dL)</b>	107.3 ± 20.9	104 (86 - 134)
<b>HDL-Cholesterol (mg/dL)</b>	29.9 ± 5.6	28.3 (20.4 - 39.4)
<b>BUN (mg/dL)</b>	16.7 ± 4.38	17.7 (14.2 - 19.8)
<b>Creatinine (mg/dL)</b>	0.82 ± 0.34	0.79 (0.49 - 1.1)
<b>eGFR (mL/min/1.73m<sup>2</sup>)</b>	90.2 ± 29.2	94.0 (70.3 - 112.9)

All patients were eligible to to participate in the study.

**3.3. Concentration of 1,5-AG and HbA1c at two time points**

The concentration of 1,5-AG after 7 days from the beginning of using CGM system during inpatient treatment was 5.98 (5.39 - 7.01) µg/mL, greater than the measurements at the beginning of the study of 2.91 (2.41 - 4.32) µg/mL, which was statistically significant  $p < 0.001$ . HbA1c concentration after 7 days was similar to the initial time and the difference was not statistically significant,  $p = 0.08$  (Table 2).

**Table 3: Concentration of 1,5-AG at the beginning of CGM system and 7 days later**

<b>N = 38</b>	<b>T0</b>	<b>T7d</b>	<b>P</b>
<b>1,5-AG (µg/mL)</b>	2.91 (2.41 - 4.32)	5.98 (5.39 - 7.01)	< 0.001*
<b>HbA1c (%)</b>	9.23 ± 2.07	9.12 ± 1.9 2	0.08**

\*: Wilcoxon Signed-rank test; \*\*: paired t test

**3.4. Correlation between 1,5-AG, HbA1c and indicators collected from the CGM system**

**Table 4: Spearman's rank correlation coefficient between 1,5-AG, HbA1c and indicators collected from the CGM system in 7 days**

<b>N = 38</b>	<b>MG</b>	<b>P</b>	<b>TIR</b>	<b>P</b>	<b>CoV</b>	<b>P</b>
<b>1,5-AG</b>	-0.64	<0.001	0.38	0.02	-0.45	0.01
<b>HbA1c</b>	0.47	0.01	-0.35	0.048	-0.27	0.13

There was a strong inverse correlation between 1,5-AG level and mean glucose in 7 days.  $r$  was -0.64 and the relationship was statistically significant,  $p < 0.001$ .

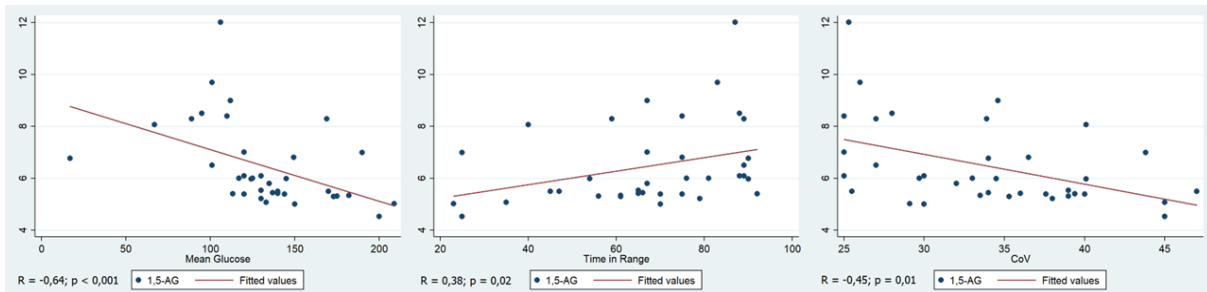
There was a moderate positive correlation between 1,5-AG level and TIR in 7 days.  $r$  was 0.38 and the relationship was statistically significant,  $p < 0.05$ .

There was a moderate inverse correlation between 1,5-AG level and the CoV of glucose for 7 days.  $r$  was -0.45 and the relationship was statistically significant,  $p < 0.05$ .

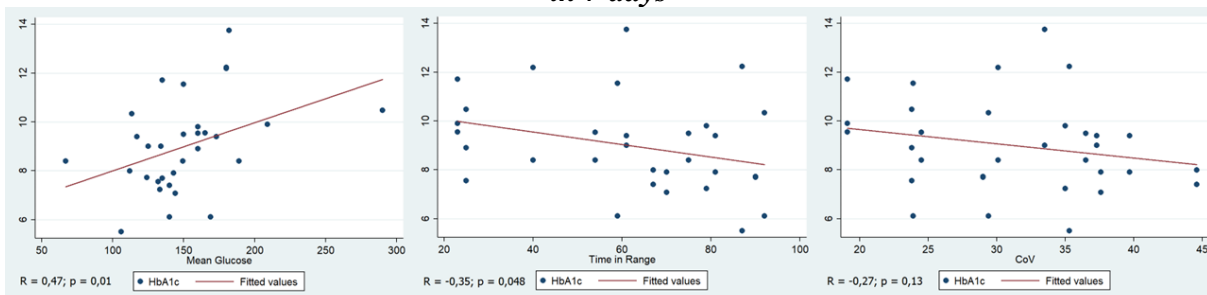
There was a moderate positive correlation between HbA1c and mean glucose in 7 days.  $r$  was 0.47 and the relationship was statistically significant,  $p < 0.05$ .

There was a moderate inverse correlation between HbA1c and TIR in 7 days.  $r$  was -0.35 and the relationship was statistically significant,  $p < 0.05$ .

There is a weak inverse correlation between HbA1c and CoV of glucose for 7 days.  $r$  was -0.27 and this correlation is not statistically significant,  $p = 0.13$ .



**Figure 1: Spearman's rank correlation between 1,5-AG and mean glucose , TIR and CoV in 7 days**



**Figure 2: Spearman's rank correlation between HbA1c and mean glucose, TIR and CoV in 7 days**

IV. DISCUSSION:

Our study followed 38 patients with type 2 diabetes who used the continuous glucose monitoring system CGM FreeStyle Libre Abbott. At 7 days from the beginning of using CGM system, we collected data on each patient's CGM system and test 1,5-AG, HbA1c for analysis, including:

- Mean glucose in 7 days: MG
- Time in Range: TIR, glycemic value in target range is 70 - 180 mg/dL [1]
- Coefficient of variation of blood glucose: CoV

Of the 3 parameters mentioned above, TIR and CoV play a role in assessing blood glucose fluctuations and there have been studies demonstrating the role of these indicators in assessing complications of diabetes.

1,5-AG had a strong inverse correlation with 7-day MG.  $r$  was  $-0.64$  and the

relationship was statistically significant  $p < 0.001$ . HbA1c had a moderate positive correlation with 7-day MG.  $r$  was  $0.47$  and the relationship was statistically significant  $p < 0.05$ . This suggests the mean glucose assessment role of 1,5-AG and HbA1c: in the short term, 1,5-AG is capable of assessing blood glucose more accurately than HbA1c.

Our study indicated that 1,5-AG had a moderate positive correlation with TIR and HbA1c had a moderate inverse correlation with TIR.  $r$  was  $0.38$  and  $-0.35$ , respectively and they were statistically significant,  $p < 0.05$ . Mana Ohigashi's (2021) [4] study on the same FreeStyle Libre Abbott system on the correlation between TIR with 1,5-AG and HbA1c per 100 patients with type 2 diabetes showed similar correlations but with stronger degree,  $r$  of  $0.56$  and  $-0.56$ ; those were statistically significant  $p < 0.05$ .

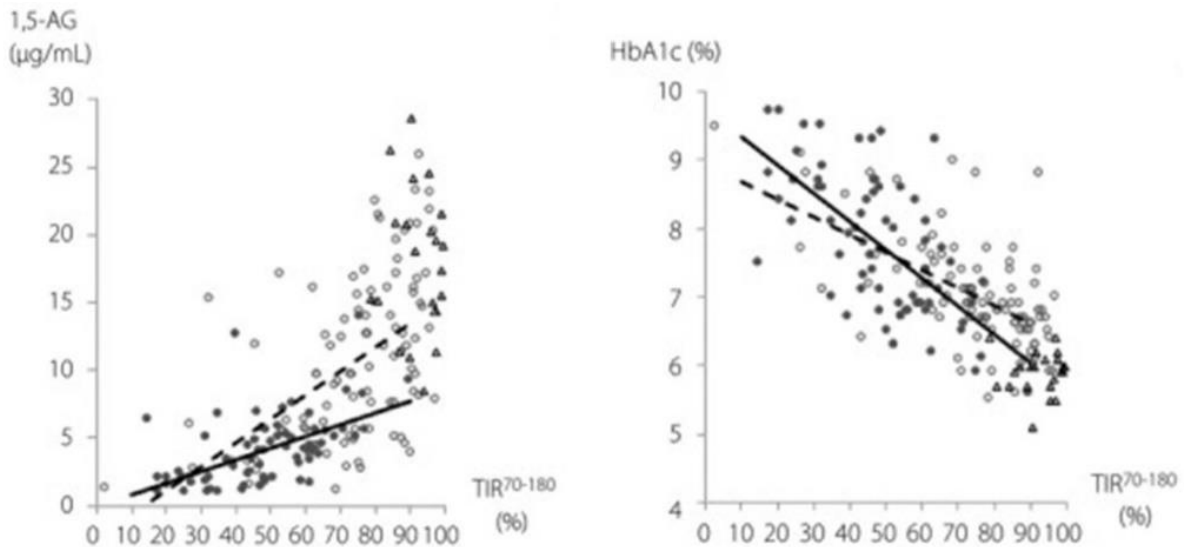


Figure 3: Correlation of TIR with 1,5-AG and HbA1c in Mana Ohigashi's study [4]



Our study indicated that 1,5-AG had a moderate inverse correlation with CoV.  $r$  was -0.45 and the relationship was statistically significant,  $p < 0.05$ . HbA1c had a weak inverse correlation with CoV.  $r$  was -0.27 and this correlation was not statistically significant,  $p = 0.13$ . The study by Mana Ohigashi (2021) [7] showed that there was a moderate correlation between CoV and 1,5-AG, HbA1c.  $r$  was -0.15 and -0.11, respectively with no statistical significance,  $p > 0.05$ .

Research by Christine L Chan (2017) [3] on 56 young patients with pre-diabetes mellitus and type 2 diabetes mellitus with Medtronic's CGM system indicated that there was a correlation between 1,5-AG, HbA1c, and indicators that evaluate blood glucose fluctuations of this CGM system such as peak glucose, area under the curve for glucose above 180 mg/dL (AUC180), standard deviation (SD), and mean amplitude of glycemic excursions (MAGE).

The study by Hannah Seok (2015) [5] on 17 type 1 diabetes patients using Medtronic's CGM system for 72 hours showed that the change of 1,5-AG was strongly correlated with glycemic excursion assessment indicators as standard deviation (SD), mean amplitude of glucose excursions (MAGE), lability index (LI), mean postmeal maximum glucose (MPMG), and area under the curve for glucose above 180 mg/dL (AUC180).  $r$  were -0.576, -0.613, -0.600, -0.630, and -0.500, respectively, all with  $p < 0.05$ . Meanwhile, the HbA1c was completely

irrelevant with the parameters for assessing glycemic variability.

The present and previous studies suggested that 1,5-AG may be an applicable marker for assessing glycemic variability and the ability to control blood glucose in short follow-up periods better than HbA1c.

#### V. CONCLUSIONS:

1,5-AG was correlated with mean glucose, TIR and CoV in 7 days ( $p < 0.05$ ). HbA1c was correlated with mean glucose and TIR but not correlated with CoV. This indicates the role of 1,5-AG in assessing glycemic variability. These results may demonstrate that 1,5-AG reflects not only average glucose but also glycemic fluctuation in short term; thus 1,5-AG may be an alternative biomarker for assessing glycemic control in type 2 diabetes patients.

#### VI. ACKNOWLEDGMENT:

We would like to express our sincere gratitude to the University of Medicine and Pharmacy at Ho Chi Minh City and Cho Ray Hospital for facilitating the completion of this study.

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