

Serum 1,5–Anhydroglucitol Serves as An Additional Biomarker for Diagnosing and Monitoring Type 2 Diabetes: Vietnamese Cohort

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Abstract:

Objective: The incidence of diabetes is increasing worldwide, at an incredible pace and with a substantial burden. Precise and early diagnosis of type 2 diabetes (T2D) can help patients control complications. It has been found that decreased levels of 1,5-anhydroglucitol (1,5-AG) in serum can serve as a marker for diagnosing and monitoring degrees of T2D. Our study validated the value of 1,5-AG in T2D patients in a Vietnamese population over their treatment course.

Material and Methods: A cohort of 100 participants; including 50 T2D patients and 50 healthy individuals were recruited from Da Nang hospital. Demographic features were recorded. Blood samples over the period of treatment were collected for measurement of 1,5-AG, fasting blood glucose, hemoglobin A1C (HbA1c) and fructosamine.

Results: Patients with T2D showed significant decreases in 1,5-AG compared to the control group: 10.91 ± 6.53 $\mu\text{g/mL}$ and 26.83 ± 9.98 $\mu\text{g/mL}$, respectively. Among T2D patients, individuals with more severe degree, as classified by kinds of treatment and control of hyperglycemic markers, demonstrated lower levels of 1,5-AG compared to patients with less severity ($p\text{-value} < 0.001$). A negative correlation was found between 1,5-AG and other hyperglycemic markers, including HbA1C ($r = -0.591$, $p\text{-value} < 0.001$), fasting blood glucose ($r = -0.431$, $p\text{-value} < 0.0001$), and fructosamine ($r = -0.482$, $p\text{-value} < 0.001$). Levels of 1,5-AG showed an increasing trend, while fasting blood glucose and other hyperglycemic markers reduced over patients receiving treatment periods.

Conclusion: Monitoring 1,5-AG could be applied as an additional biomarker to strengthen diagnosis and provide efficacious follow-up on T2D patients.

Keywords: 1,5-anhydroglucitol, biomarker, glycemic control, type 2 diabetes

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Introduction

Diabetes mellitus has emerged as a significant concern, impacting the well-being of individuals. According to projections made by the International Diabetes Federation, the global count of individuals afflicted with diabetes is expected to reach a staggering 552 million by 2030. The World Health Organization estimated that in the Southeast Asia Region, over 96 million individuals are affected by diabetes, with an additional 96 million being in a pre-diabetic state. This leads to a minimum of 600,000 deaths annually. It is concerning to note that half of the adults suffering from type 2 diabetes (T2D) remain undiagnosed¹. Moreover, the number of individuals with pre-diabetes was three times higher than those diagnosed with diabetes.

Achieving good control of blood glucose is a crucial goal in the therapy of various diabetes forms. The continuous monitoring of blood glucose is essential to attain treatment goals²; wherein it has been previously reported that approximately 50.0% of patients successfully achieve their treatment goals. Additionally, merely 30.0% of patients are able to sustain glucose control over an extended period of time³. Currently, hemoglobin A1C (HbA1c) is commonly utilized as the primary indicator for glycemic control in clinical settings. While HbA1c provides insight into the long-term state of glycemic control (over the past 1–2 months), it may not accurately represent changes in glycemic control over the short term. It is important to note that patients with hematological conditions like anemia and variant hemoglobin may exhibit abnormal HbA1c values. In addition to this, HbA1c predominantly reflects average plasma glucose levels only and does not capture postprandial plasma glucose fluctuations⁴. Another widely used marker for monitoring hyperglycemia is fructosamine⁵. Fructosamine is well known as a marker indicating concentration of blood sugar over a period of 2–3 weeks, as the general half-life of albumin in

blood⁶. Taken together, these indices remain disadvantages, as the indicators merely provide a snapshot of blood glucose levels at a specific moment or an average representation of the glucose index value over a duration of 2–3 months, or even weeks⁷.

Another biomarker is 1,5-anhydroglucitol (1,5-AG) – a monosaccharide sharing a comparable structure with glucose, which undergoes competition with glucose for reabsorption in the renal tubules. 1,5-AG serves as the exclusive metabolite of 1,5-anhydrofructose (1,5-AF) within the human body. It is formed through the reduction of 1,5-AF, a compound continuously synthesized by ligases originating from glycogen in various tissues, such as the liver, muscle, and kidney⁸. However, 1,5-AF is hardly detected in human blood, because it is rapidly converted into the reduced form of 1,5-AG⁹. Circulating 1,5-AG is eliminated by the kidneys and subsequently reabsorbed through the sodium-glucose co-transporter 4 (SGLT4) located in the renal proximal tubules^{4,10}. While this cotransporter primarily reabsorbs glucose expelled by the glomeruli, it can also facilitate the reabsorption of 1,5-AG. Consequently, individuals with urinary glucose levels surpassing the normal physiological range will experience a deficiency in SGLT4's ability to reabsorb 1,5-AG, leading to reduced levels of this metabolite in serum^{11–13}. The levels of 1,5-AG rise in diabetes patients when blood glucose control situations are well-managed and vice versa. This biomarker, 1,5-AG, serves as an indicator of the spike in postprandial blood glucose and fluctuations in blood glucose levels within a span of 1 to 2 weeks. Notably, during this time frame, neither fructosamine nor HbA1C have exhibited any changes^{14,15}. 1,5-AG serves as a marker for intermediate- or short-term glycemic control and is not impacted by hemoglobin metabolism. Hence, 1,5-AG is recognized for its ability to reflect postprandial plasma glucose levels⁴.

The glycemic biomarkers could vary among different ethnicities. A previous study demonstrated that both HbA1c and 1,5-AG can be different between Caucasians and non-Caucasian ethnic groups¹⁶. This study aimed to evaluate the average value of serum 1,5-AG in T2D patients and non-diabetic individuals in Da Nang, a city located in the central coastal region of Vietnam. Additionally, it analyzed the correlation of serum 1,5-AG levels with other indicators of glucose monitoring (blood glucose levels, HbA1c, and fructosamine) over a treatment course of 8 weeks. The results could potentially provide a more profound understanding of the variation in 1,5-AG index among T2D patients undergoing treatment, as well as in comparison to individuals without diabetes, in both biological sex groups. Additionally, this study may aid in assessing the efficacy of utilizing 1,5-AG as a biomarker for monitoring and evaluating the duration of T2D treatment in an Asian population, particularly when compared to other existing biomarkers.

Material and Methods

Research ethics issues and sample population

The research conducted in this study followed the principles set forth in the Declaration of Helsinki. Authorization for the study was provided by the Biomedical Ethics Committee of DaNang University of Medical Technology and Pharmacy, in addition to the Board of Directors of DaNang Hospital: reference number 1391/BVDN-HDYD, issued on October 29th 2020. We prepared written informed consent from patients and/or their family members (legal representatives) to join the study (of the patient). All information taken from electronic medical records was only used for research. Patients were free to decline or stop participating in the study at any time. The research was conducted on the population of patients hospitalized from April 1st, 2020 to March 1st, 2022. Patients

were assigned an identifier and had their names coded instead of being compiled. All data collected from research questionnaires was encrypted and kept private. Research data was only accessible to the leader of the research team.

Participants

This research study recruited 100 participants, randomly that consented to participate; including 2 groups with 50 people per group (diabetes vs non-diabetes volunteers), for which the population sampling formula was calculated from a previous study¹⁴. Diabetes patients were diagnosed and treated based on the American Diabetes Association 2019 guidelines (American Diabetes Association–Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes–2019)¹⁷ and the Guidelines for diagnosis and treatment of T2D from the Vietnamese Ministry of Health–issued with the decision No. 5481/QD-BYT, dated December 30, 2020¹⁸. Patients that could begin their own treatment (chemical therapy) at the research start–point or previously (with the treatment target of bringing the glycemic situation back to control status, with the value of HbA1c <7.0%, and a fasting plasma glucose in the range of 4,4–7,2 mmol/L) were recruited. After diagnosis, all 50 patients in the study were monitored and followed up in an outpatient setting. This research population excluded the patients having met at least one of these criteria as follows: pregnant women, type 1–diabetes patients, T2D patients with comorbidities (kidney failure, cirrhosis, gastric bypass, malignant tumors, pancreatic tumors, leukemia, collagen disease, gout and so forth) or those with severe complications hospitalized in a coma due to dramatically increased or decreased blood glucose and requiring monitoring and treatment. T2D patients treated with sodium–glucose co–transporter 2 inhibitor drugs or those using oriental medicine, herbal functional foods (*Polygala tenuifolia* Willd. or *Polygala senega* L. and *Polygala senega*

L. var. latifolia Torrey et Gray, family Polygalaceae)^{19–21}, T2D patients with a creatinine index value $>32 \mu\text{mol/L}$ and estimated glomerular filtration rate of $<60\text{mL/min/1.73 m}^2$ ^{19,20}. The control group consisted of volunteers participating in the study, who did not have diabetes and blood glucose disorders (fasting plasma glucose $<5.6 \text{ mmol/L}$ and/or HbA1c $<5.7\%$), with a similar age and sex distribution equivalent to the diabetes group. Exclusion criteria for the control group were pregnant women, or individuals with specific medical history (gout, chronic liver disease, kidney disease, malignant disease or have had gastric surgery), or those using oriental medicine and herbal functional foods (*Polygala tenuifolia* Willd. or *Polygala senega* L. and *Polygala senega* L. var. *latifolia* Torrey et Gray, family Polygalaceae)^{19–21}. Individuals were categorized as hypertensive when their systolic blood pressure was $\geq 140 \text{ mmHg}$ and/or their diastolic blood pressure was $\geq 90 \text{ mmHg}$, or when being treated as a hypertension patient; as per physician request^{22,23}.

Clinical characteristics and laboratory measurements

Information on the clinical features of the individuals, including age, weight, vital signs (systolic blood pressure, diastolic blood pressure), BMI, waist/hip ratio, medical profile marks (medical history with hypertension, dyslipidemia), family history (diabetes, hypertension) and the living routines of smoking and alcohol consumption was collected. Blood samples collected from participants were promptly used for the measurement of glycemic markers. The equipment was calibrated with an internal control for consistent measurement. The laboratory parameters including; plasma glucose, fructosamine and 1,5-AG, were assessed using the BECKMAN COULTER AU480 analyzer system (Brea, CA, USA), with the glucose test kit ORS6121 from

Beckman Coulter (Brea, CA, USA), 1,5-AG test using the commercial GlycoMark™ kit (Tomen America, New York, NY) and a fructosamine test using the fructosamine test (Biosystem S.A., Spain). HbA1c was tested via the HPLC principle by the Premier Hb9210 system (Trinity Biotech, Bray, Co.Wicklow, Ireland).

Statistical analysis

IBM statistical package for social sciences version 20 (IBM, Armonk, New York, USA), Excel 2010 (Microsoft, Redmond, Washington), and MedLab software ver. 12.5 (MedCalc Software Ltd, Ostend, Belgium) was utilized for statistical calculation. We compared two mean values by t-tests and Man-Whitney, compared two percentages by Chi-squared (χ^2) test and Fisher test, and also used for ordinal variables. We set the statistical significance at a value of $p\text{-value} < 0.05$, and also calculated the odds ratios and their 95.0% confidence intervals. Figures were plotted by the program R (open-source program, version 4.3.0).

Results

Demographic, clinical, and laboratory data of the research cohort

Amongst subjects participating in this study, group T2D patients indicated a higher incidence of hypertension, dyslipidemia, and elevated waist/hip ratios, with a $p\text{-value} < 0.05$ (Table 1). Risk factors, including smoking and regular alcohol consumption, were observed in the T2D group with a greater proportion compared to the control group. Notably, the T2D group displayed elevated frequencies of family history for diabetes (46.0%), hypertension (52.0%), and both conditions (34.0%), all of which were significantly higher, with a $p\text{-value} < 0.05$.

Table 1 Demographics, medical history, epidemiological factors and laboratory test results

Category	Diabetes group n (%)	Control group n (%)	p-value
Gender			
Male	28 (56.0)	23 (46.0)	ns
Female	22 (44.0)	27 (54.0)	
Age group			
≥60	18 (36.0)	10 (20.0)	ns
<60	32 (64.0)	40 (80.0)	
Average age (mean±S.D.)	55.94±7.84	52.86±7.90	
Duration of diabetes (yrs)	6.10±5.50		
BMI group			
Normal and low weight	18 (36.0)	32 (66.0)	
Overweight and obesity	32 (64.0)	18 (36)	
Average BMI	24.20±3.10	22.40±2.00	
Blood pressure (research's test)			
Normal	26 (52.0)	39 (78.0)	
Hypertension	24 (48.0)	11 (22.0)	*
SBP	130.40±14.60	116.40±14.90	*
DBP	84.20±7.97	79.50±10.35	*
Waist/hip ratio	0,93±0,07	0,88±0,06	*
Current smoker	13 (26)	4 (8)	*
Alcohol consumer	14 (28)	6 (12)	*
Hypertension (patient profile)	25 (50)	7 (14)	*
Dyslipidemia (patient profile)	27 (54)	7 (14)	*
Family medical history			
Diabetes	23 (46)	10 (20)	*
Hypertension	26 (52)	15 (30)	*
Diabetes+Hypertension	17 (34)	5 (10)	*
Glucose (mmol/L) (Mean±S.D.)	7.66±2.10	4.46±0.76	*
HbA1c (%) (Mean±S.D.)	7.51±1.43	5.54±0.21	*
Fructosamine (μmol/L) (Mean±S.D.)	323±82	256±31	*
1,5-Anhydroglucitol (μg/mL) (Mean±S.D.) (Day 1)			
Mean value	10.91±6.53	26.83±9.98	*
Sex			
Male	12.66±7.32	31.31±10.21	***
Female	8.68±4.60	23.02±8.17	
Age group			
<60	11.84±6.93	27.26±10.56	***
≥60	9.26±5.55	25.11±7.41	

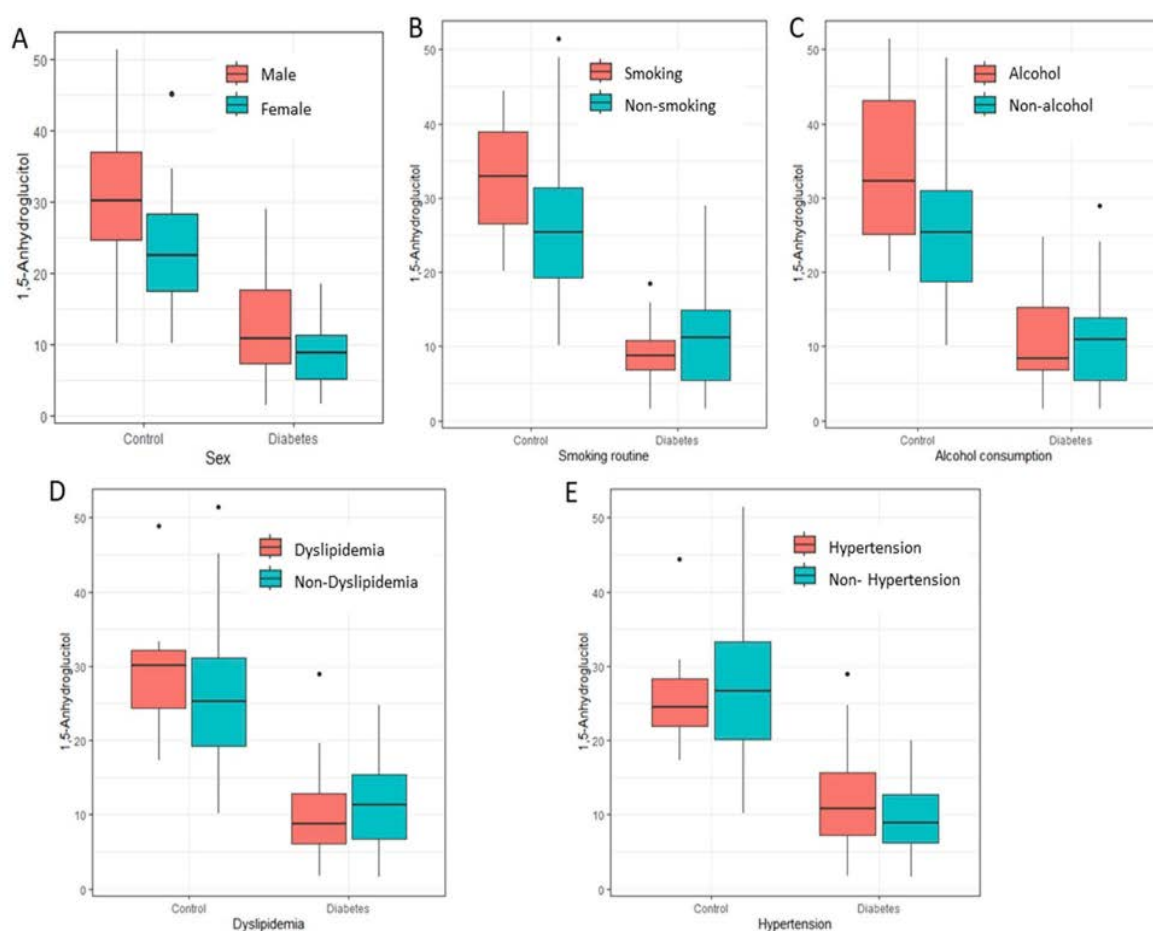
ns=not significant, S.D.=standard deviation, yrs=years, BMI=body mass index, SBP=systolic blood pressure, DBP=diastolic blood pressure

*p-value<0.05, **p-value<0.01, ***p-value<0.001

Decreased 1,5-AG in serum serves as a biomarker for diagnosing T2D, but is not affected by other risk factors

There was a significant difference in glycemic markers between the T2D and the control groups. The 1,5-AG test results of both the T2D and control group were 10.91 ± 6.53 and 26.83 ± 9.98 $\mu\text{g/mL}$ (mean value $\pm$ S.D.), respectively (Table 1). Concentration 1,5-AG in the T2D group was approximately 2.46 times lower in comparison to the control group. The level of 1,5-AG upon different factors, including gender, smoking, and alcohol consumption, was

further compared among participant in the research. It was noted that females showed slightly lower 1,5-AG compared to their male counterparts, within the T2D and control groups (Figure 1A). Remarkably, 1,5-AG levels showed a slight increase in the control group with smoking or alcohol consumption, suggesting these risk factors might interfere with the level of 1,5-AG in the healthy subjects; whereas, there was no difference in the T2D group (Figure 1-B, C). Dyslipidemia and hypertension in medical history showed no impact on the 1,5-AG levels within both control and T2D groups (Figure 1D, E).



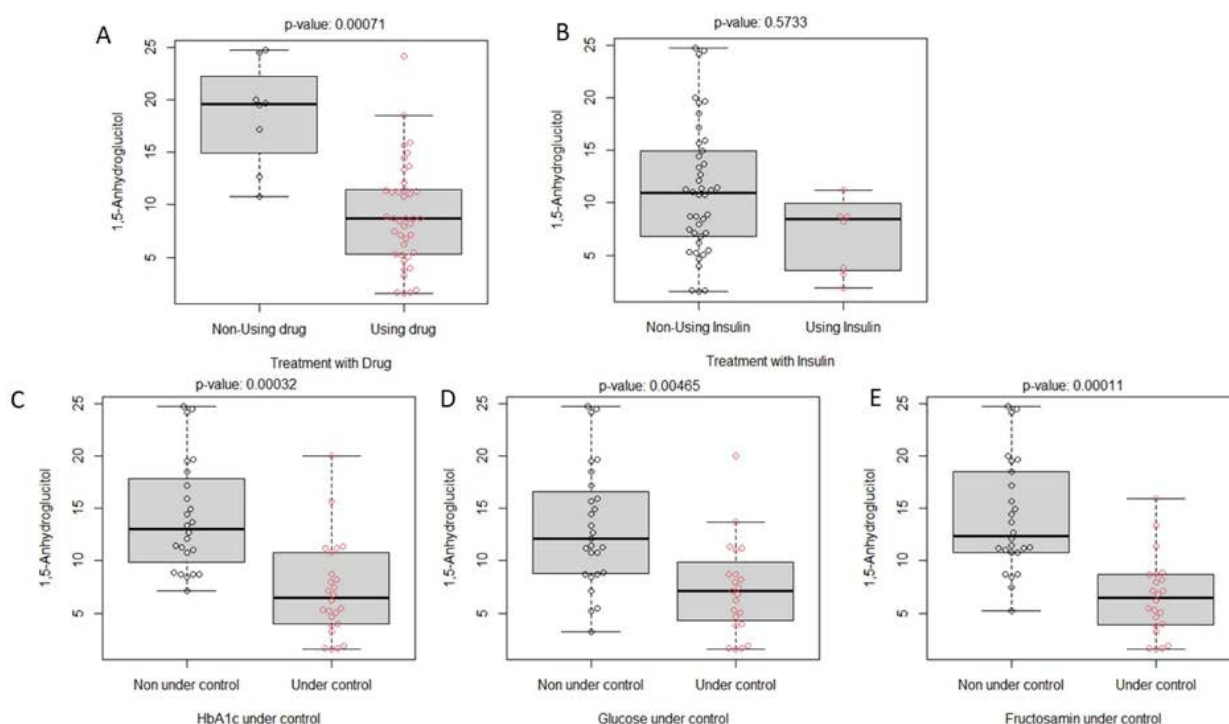
(A) biological sex, (B) smoking routine, (C) alcohol consumption, (D) Dyslipidemia, (E) hypertension

Figure 1 Comparison of 1,5-Anhydroglucitol concentration between healthy participants as the “Control” group and patients with type 2 diabetes as the “Diabetes” group, with internal comparison upon different factors

The low level of 1,5-AG in serum is associated with the severity of disease amongst T2D patients

To further investigate if whether levels of serum 1,5-AG could be utilized as a quantitative ladder for the severity of T2D, the comparison of 1,5-AG between different degrees of T2D was performed. Amongst patients with T2D, patients requiring drugs showed lower levels than those without the need for drugs (p -value<0.001, Figure 2A). The T2D subjects with insulin treatment had low levels of 1,5-AG compared to the non-insulin treated patients, although this

was not significant (Figure 2B). These data indicate lower 1,5-AG illustrated a larger degree of severity of T2D. We also compared the levels of 1,5-AG between T2D patients whose glycemic markers were well-managed and those not under control. As expected, measurement of serum 1,5-A,G of patients with uncontrolled glycemic markers, including HbA1C, glucose, and fructosamine, indicated significantly lower levels compared to patients under control (p -value<0.001, Figure 2C-E).



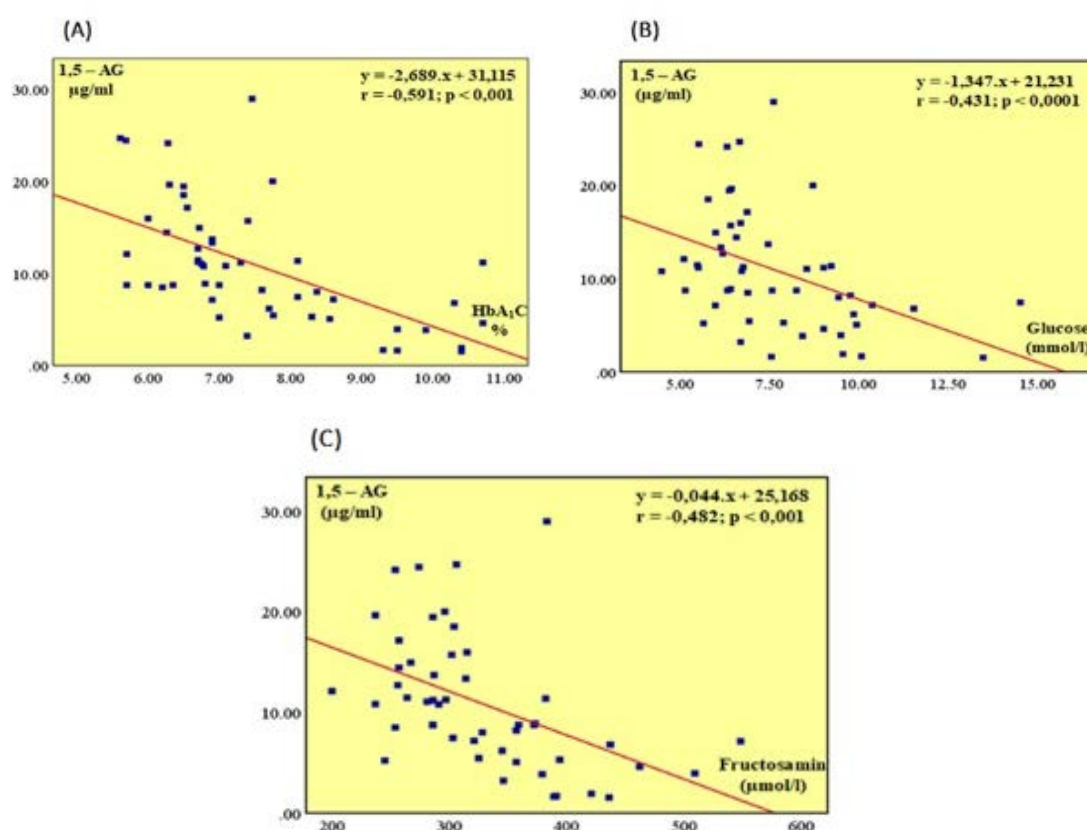
(A) patients requiring treatment with/without oral diabetes drugs, (B) patients requiring treatment with/without insulin injection, (C) patients with levels of HbA1c under/non-under control, (D) patients with levels of fasting glucose under/non-under control, (E) patients with levels of fructosamine under/non-under control. Normality of data was determined by the Shapiro-Wilk test, with p -value<0.05, and statistical comparison was performed using an unpaired t-test

Figure 2 Comparison of 1,5-Anhydroglucitol concentration in patients with type 2 diabetes upon different factors

Serum 1,5-AG could serve as an additional biomarker for T2D diagnosis

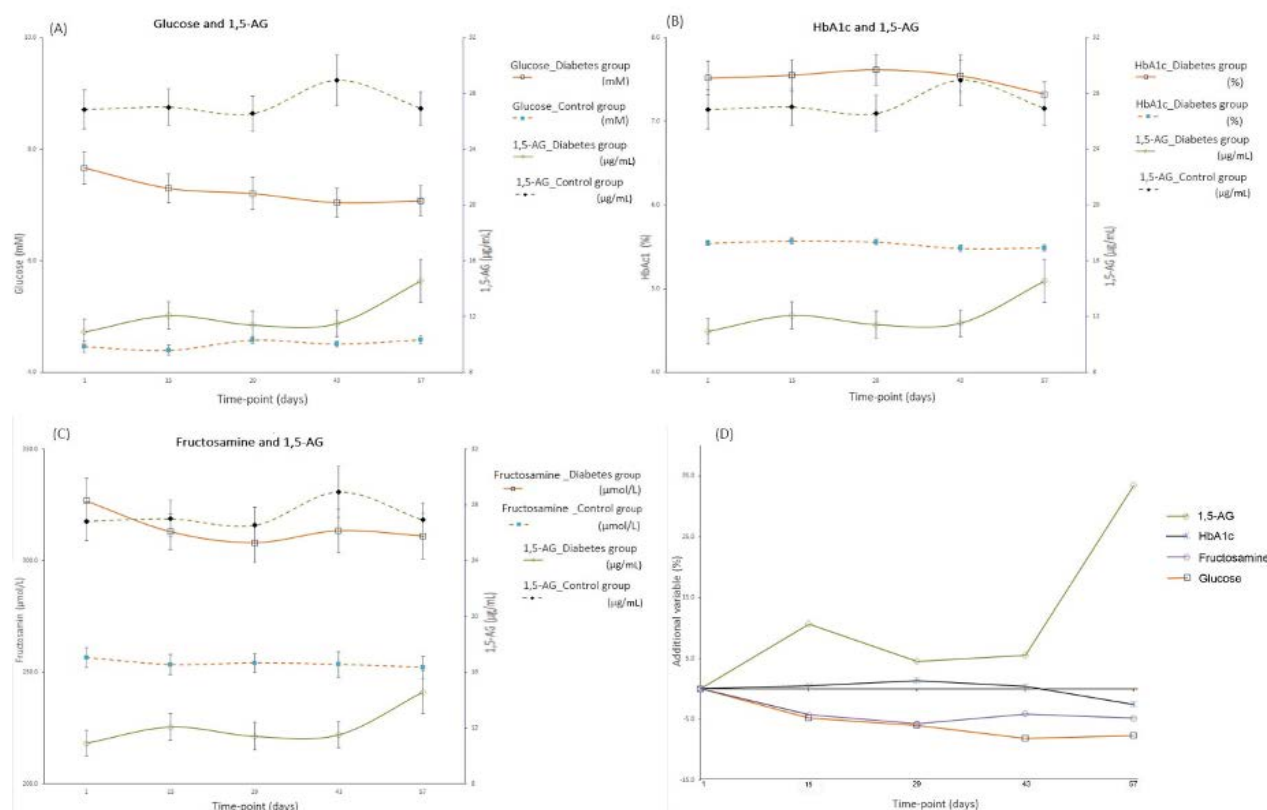
The correlations between serum 1,5-AG and other glycemic markers were evaluated among 50 Vietnamese patients with T2D. It also identified a robust, inverse relationship between 1,5-AG and HbA_{1c} levels in T2D patients ($r = -0.591$, $p\text{-value} < 0.01$). In addition to a significant negative correlation between 1,5-AG concentration and fasting blood glucose ($r = -0.431$, $p\text{-value} < 0.01$), a moderate inverse correlation was noted between 1,5-AG and fructosamine levels ($r = -0.482$, $p\text{-value} < 0.01$) (Figure 3). Moreover, the kinetic changes

in concentration of biomarkers, including glucose, HbA_{1c}, and fructosamine, compared to changes of 1,5-AG were monitored over an 8-week treatment course (Figure 4A–C). The concentration of 1,5-AG showed an increasing trend while other hyperglycemic markers reduced over the period of treatment, suggesting 1,5-AG could be applied for assessment of patient response to treatment. Notably, 1,5-AG exhibited the greatest gaps among the other indices, by comparing values at the ending points of treatment to the values at their initial point. This suggests 1,5-AG is a more sensitive marker to assess the treatment of T2D.



(A) HbA_{1c}, (B) fasting glucose and, (C) fructosamine, of patients with type 2 diabetes

Figure 3 Correlation of the concentration changes of 1,5-AG with other biomarkers



(A), HbA1c (B), and fructosamine (C), in comparison to 1,5-AG (value point=mean±SEM); (D) percentage of additional variables (over the value of day 1) of all 4 indices over the therapy-period in the T2D group)

Figure 4 The concentration changes of four biomarkers (glucose, HbA1c, fructosamine, 1,5-AG) over an 8-week treatment course; including concentration of glucose

Discussion

Effective management of blood glucose levels is a fundamental aspect of treating diabetes. We found that a decrease in 1,5-AG concentration serves as a significant indicator of hyperglycemia in diabetic patients⁴.

In our study, individuals diagnosed with T2D exhibited an average 1,5-AG concentration of 10.91 ± 6.53 µg/mL, which was notably lower, by 2.46 times, than the control group's concentration of 26.83 ± 9.98 µg/mL. This disparity in 1,5-AG concentration between the two groups was statistically significant (p -value<0.001). Within this investigation, individuals diagnosed with T2D exhibited 1,5-

AG levels of 12.66 ± 7.32 µg/mL for males and 8.68 ± 4.60 µg/mL for females. The concentration of 1,5-AG in both males and females within the disease cohort was notably lower compared to the control group, with statistical significance (p -value<0.001).

This study aimed to apply a mixture of fasting blood glucose, HbA1c, and fructosamine to gauge the extent of blood glucose control within the study cohort. Our data demonstrated consistent of decreased levels of 1,5-AG in T2D patients in comparison with healthy controls (Figure 1), which is consistent with previous studies in other populations^{14,24,25}. Moreover, it is interesting that T2D patients

with higher degrees showed lower levels of 1,5-AG than those with glycemia under control (Figure 2). It was found that their 1,5-AG showed significantly negative correlation with three of the hyperglycemic biomarkers, including HbA1c, glucose, and fructosamine suggesting the validity of 1,5-AG as an additional marker for T2D diagnosis (Figure 3).

Fasting blood glucose, which is the level of blood glucose measured after fasting for a certain period of time (approximately 8–12 hours), is a biochemical marker widely used for diagnosing and monitoring diabetes, or prediabetes. In our research, we observed that the concentration of 1,5-AG in the T2D group, whose fasting blood glucose levels met the treatment goal, was 13.27 ± 5.83 $\mu\text{g/mL}$ (Supplementary Table 1). This value was higher compared to the group whose fasting blood glucose levels did not meet the treatment target, having had a concentration of 8.13 ± 6.30 $\mu\text{g/mL}$ ($p\text{-value} < 0.01$) (Supplementary Table S1). 1,5-AG is structurally similar to glucose and is reabsorbed in the renal tubules by a competitive channel with glucose. Consequently, patients with consistently high blood glucose levels, even without diabetes, often exhibit low levels of 1,5-AG. It has been reported that the reduction in blood 1,5-AG levels could be detected before an increase in blood glucose, which serves as a predictable marker for monitoring diabetes²⁶. While fasting blood glucose testing is straightforward, this index has a drawback due to its inability to reflect past glucose fluctuations, thereby hindering clinicians from making a comprehensive evaluation before recommending treatment. The findings from our study propose that 1,5-AG may address this limitation, even among individuals with fasting blood glucose levels within the desired range (Figure 4). Hence, enhancing the efficacy of blood glucose management in diabetic patients.

Throughout the period of treatment, we continuously monitored blood glucose during the control process as well as fluctuations in glycemic indices among individuals

diagnosed with T2D. The indices, including 1,5-AG, HbA1c, glucose (fasting blood) and fructosamine, were repeatedly measured at specific time points: bi-weekly from the beginning of the study. Our findings revealed a notable decrease in blood glucose, HbA1c, and fructosamine levels of most patients after 8 weeks of treatment, indicating a positive response to the treatment regimen (Figure 4A–C). Additionally, we conducted pairwise comparisons of blood glucose control indices after 2 weeks of treatment to assess the changes in blood glucose control over a two-week period in individuals with T2D. The results indicated significant alterations in fructosamine levels between weeks 2 and 4 ($p\text{-value}^{2,3} < 0.05$) as well as in HbA1c levels between weeks 6 and 8 ($p\text{-value}^{4,5} < 0.05$) (Supplementary Tables 2,3,4). Notably, the 1,5-AG index exhibited changes from week 2, 4, and week 8 ($p\text{-value}^{1,2} < 0.05$; $p\text{-value}^{4,5} < 0.05$) (Supplementary Tables 2,3,4). Furthermore, the data indicated a substantial alteration of the 1,5-AG index on both day 15 and especially day 57, while the other indices displayed less fluctuations (Figure 4D). This distinct change could potentially be attributed to the early reaction of the 1,5-AG during treatment. The sensitivity of 1,5-AG demonstrated the advantage in monitoring and evaluating diabetes through the favorable trajectory of the treatment regimen, thereby offering potential benefits to individuals with T2D under therapy. While our data was collected and analyzed on human samples obtained in a hospital setting, limitations in our study remain. Primarily, our study cohort was restricted to patients recruited from a single hospital, with a relatively small sample size in Vietnam. Thus, the characteristics of this cohort may not fully represent the broader population within the region. In addition, while environmental factors, including nutrition and pollution, might affect diabetes development, our study lacks some details of these external risk factors for better control to compare 1,5-AG levels.

Conclusion

To conclude, in addition to conventional markers, including fasting blood glucose, HbA1C and fructosamine, our study has validated 1,5-AG as a useful index for diagnosing and monitoring T2D in a Vietnamese cohort of Southeast Asia.

Author contributions

Study concept and design: TTL; acquisition of data: LTHN; analysis and interpretation of data: VC, CPD; drafting of the manuscript: VC, CDP, and TTL; statistical analysis: LTHN, and CPD; and study supervision: TTL.

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Conflict of interest

The authors disclose no conflicts.

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Supplementary Table 1: 1,5-AG values in groups of treatment outcome

Blood glucose control indicators		1,5-AG (µg/mL) (Mean±S.D.)	p-value
HbA1c	Meet the treatment target	14,18±5,30	**
	Not meet the treatment target	7,89±6,13	
Glucose	Meet the treatment target	13,27±5,83	**
	Not meet the treatment target	8,13±6,30	
Fructosamin	<312 µmol/L	14,15±5,39	**
	<312 µmol/L	7,40±5,87	

**p-value<0.01, S.D.=standard deviation

Supplementary Table 2: Values of blood glucose control indicators in the research duration in the T2D group

Time-point	1,5-AG (Mean±S.D.)	HbA1c (Mean±S.D.)	Glucose (Mean±S.D.)	Fructosamine (Mean±S.D.)
T1 (day 1)	10.91±6.53	7.51±1.43	7.66±2.09	326±72
T2 (day 15)	11.40±7.05	7.55±1.35	7.30±1.83	313±57
T3 (day 29)	11.51±6.75	7.61±1.30	7.20±2.10	308±62
T4 (day 43)	12.07±6.89	7.55±1.35	7.04±1.84	313±69
T5 (day 57)	14.56±10.54	7.32±1.04	7.07±1.90	311±73
p-value	p-value (1,2)*	p-value (1,2)-ns	p-value(1,2)-ns	p-value (1,2)-ns
	p-value (2,3)-ns	p-value (2,3)-ns	p-value (2,3)-ns	p-value (2,3)*
	p-value (3,4)-ns	p-value (3,4)-ns	p-value (3,4)-ns	p-value (3,4)-ns
	p-value (4,5)*	p-value (4,5)*	p-value (4,5)-ns	p-value (4,5)-ns

*p-value<0.05, ns=not significant, S.D.=standard deviation

Supplementary Table 3: Values of blood glucose control indicators in the research duration in the T2D group–meet the treatment target

Time–point	1,5-AG (Mean±S.D.)	HbA1c (Mean±S.D.)	Glucose (Mean±S.D.)	Fructosamine (Mean±S.D.)
T1 (day 1)	14.18±5.30	6.39±0.42	6.32±0.85	294±66
T2 (day 15)	15.93±6.20	6.45±0.51	6.34±1.00	291±46
T3 (day 29)	13.79±6.34	6.68±0.50	6.28±1.15	278±48
T4 (day 43)	13.88±6.78	6.71±0.61	6.39±0.97	292±45
T5 (day 57)	20.17±12.00	6.63±0.68	6.60±1.30	274±64
	p–value (1,2)*	p–value (1,2)–ns	p–value (1,2)–ns	p–value (1,2)–ns
	p–value (2,3)*	p–value (2,3)–ns	p–value (2,3)–ns	p–value (2,3)–ns
p–value	p–value (3,4)–ns	p–value (3,4)–ns	p–value (3,4)–ns	p–value (3,4)–ns
	p–value (4,5)*	p–value (4,5)–ns	p–value (4,5)–ns	p–value (4,5)–ns

*p–value<0.05, ns=not significant, S.D.=standard deviation

Supplementary Table 4: Values of blood glucose control indicators in the research duration in the T2D group–not meeting the treatment target

Time–point	1,5-AG (Mean±S.D.)	HbA1c (Mean±S.D.)	Glucose (Mean±S.D.)	Fructosamine (Mean±S.D.)
T1 (day 1)	8.89±6.15	8.54±1.25	8.90±2.13	356±65
T2 (day 15)	9.40±5.49	8.47±1.22	8.19±1.99	353±59
T3 (day 29)	9.20±7.06	8.47±1.23	8.06±2.39	335±63
T4 (day 43)	9.33±6.05	8.30±1.39	7.64±2.24	333±81
T5 (day 57)	9.37±6.66	7.96±0.92	7.52±2.27	345±65
	p–value (1,2)*	p–value (1,2)–ns	p–value (1,2)–ns	p–value (1,2)–ns
	p–value (2,3)–ns	p–value (2,3)–ns	p–value (2,3)–ns	p–value (2,3)–ns
p–value	p–value (3,4)–ns	p–value (3,4)*	p–value (3,4)–ns	p–value (3,4)–ns
	p–value (4,5)–ns	p–value (4,5)*	p–value (4,5)–ns	p–value (4,5)–ns

*p–value<0.05, ns=not significant, S.D.=standard deviation

Supplementary Table 5: Values of blood glucose control indicators in the research duration in the control group

Time–point	1,5-AG (Mean±S.D.)	HbA1c (Mean±S.D.)	Glucose (Mean±S.D.)	Fructosamine (Mean±S.D.)
T1 (day 1)	26.83±9.98	5.54±0.21	4.46±0.76	256±31
T2 (day 15)	26.55±9.13	5.57±0.24	4.39±0.62	253±32
T3 (day 29)	28.93±12.99	5.55±0.26	4.37±0.45	254±29
T4 (day 43)	27.02±9.40	5.48±0.24	4.50±0.39	254±41
T5 (day 57)	26.93±8.64	5.49±0.30	4.58±0.47	252±35
	p–value (1,2)–ns	p–value (1,2)–ns	p–value (1,2)–ns	p–value (1,2)–ns
	p–value (2,3)–ns	p–value (2,3)–ns	p–value (2,3)–ns	p–value (2,3)–ns
p–value	p–value (3,4)–ns	p–value (3,4)–ns	p–value (3,4)–ns	p–value (3,4)–ns
	p–value (4,5)–ns	p–value (4,5)–ns	p–value (4,5)–ns	p–value (4,5)–ns
	p–value (1,5)–ns	p–value (1,5)–ns	p–value (1,5)–ns	p–value (1,5)–ns

*p–value<0.05, ns=not significant, S.D.=standard deviation