The Diagnostic Value of Serum 1,5-Anhydroglucitol in Type 2 Diabetes Mellitus: a Cohort study in Da Nang city

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ABSTRACT

Background: Type 2 diabetes mellitus (T2D) is a growing global health concern, with effective biomarkers needed for early diagnosis and management. Serum 1,5-anhydroglucitol (1,5-AG) is a promising marker reflecting short-term glycemic control. ***Methods:*** A cross-sectional study was conducted on 61 T2D patients and 40 age- and sex-matched healthy controls at Da Nang Hospital from September 2019 to May 2020. Clinical data and laboratory results for 1,5-AG, fasting plasma glucose, HbA1c, and fructosamine were collected. ***Results:*** The mean serum 1,5-AG concentration in T2D patients was 11.3 ± 8.0 µg/mL, significantly lower than in controls (27.2 ± 9.7 µg/mL, $p < 0.01$). The 1,5-AG index showed good diagnostic performance for T2D, with an area under the ROC curve (AUC) of 0.897, sensitivity of 80.3%, specificity of 87.5%, and a diagnostic cutoff of 17.0 µg/mL. Negative correlations were observed between 1,5-AG and HbA1c ($r = -0.512$, $p < 0.01$), fasting glucose ($r = -0.467$, $p < 0.01$), and fructosamine ($r = -0.489$, $p < 0.01$). ***Conclusion:*** Serum 1,5-AG is a valuable biomarker for diagnosing T2D, offering good sensitivity and specificity in a Vietnamese population.

Keywords: 1,5-Anhydroglucitol, Type 2 Diabetes Mellitus, Glycemic Control, Biomarker, Diagnosis

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INTRODUCTION

Diabetes mellitus, particularly type 2 diabetes (T2D), is a major global health challenge, with an estimated 552 million cases projected by 2030 according to the International Diabetes Federation [1]. In Vietnam, approximately 5.5% of the population (3.5 million people) was affected by diabetes in 2017, with a significant proportion undiagnosed [2]. Effective glycemic control is critical to prevent complications, and biomarkers such as fasting plasma glucose, hemoglobin A1c (HbA1c), and fructosamine are routinely used to monitor blood glucose levels [3]. However, these markers have limitations: HbA1c reflects long-term (1–2 months) glycemic control but is less sensitive to short-term fluctuations, while fructosamine indicates glycemic status over 2–3 weeks but may be affected by serum protein levels [4,5].

Serum 1,5-anhydroglucitol (1,5-AG), a monosaccharide structurally similar to glucose, has emerged as a novel biomarker for short-term glycemic control [6]. 1,5-AG is primarily reabsorbed in the renal proximal tubules via sodium-glucose co-transporter 4 (SGLT4), competing with glucose [7]. In hyperglycemia, elevated urinary glucose inhibits 1,5-AG reabsorption, leading to reduced serum 1,5-AG levels [8]. Unlike HbA1c, 1,5-AG is

sensitive to postprandial glucose spikes and reflects glycemic excursions over 1–2 weeks, providing complementary information [9]. Additionally, 1,5-AG is unaffected by hemoglobin metabolism, making it suitable for patients with hematological disorders [10].

Despite its potential, research on 1,5-AG in Vietnam remains limited. This study aims to evaluate the diagnostic value of serum 1,5-AG for T2D in a Vietnamese population, comparing its performance with conventional biomarkers and establishing a diagnostic cut-off value.

MATERIALS AND METHODS

Study Design

This was a cross-sectional study with a control group, conducted at Da Nang Hospital from September 1, 2019, to May 30, 2020.

Participants

The study included 61 patients diagnosed with T2D based on the American Diabetes Association (ADA) 2019 guidelines [11] and Vietnamese Ministry of Health criteria (Decision No. 5481/QD-BYT, 2020) [12], and 40 healthy volunteers matched for age and sex.

Inclusion criteria for T2D group: Patients diagnosed with T2D, treated as outpatients, and willing to participate.

Exclusion criteria for T2D group: Pregnant women, patients with type 1 diabetes, comorbidities (e.g., kidney failure, cirrhosis, gastric bypass, malignant tumors, pancreatic tumors, leukemia, collagen diseases, gout), or those using SGLT2 inhibitors or herbal medicines (e.g., Polygala tenuifolia).

Inclusion criteria for control group: Volunteers without diabetes or glucose disorders (fasting plasma glucose < 5.6 mmol/L and/or HbA1c < 5.7%), matched for age and sex.

Exclusion criteria for control group: Pregnant women, individuals with gout, chronic liver or kidney disease, malignancies, gastric surgery, or use of herbal medicines (e.g., Polygala tenuifolia).

Sample Size

The sample size was calculated using the formula for comparing two means, based on a previous study by Wang et al. [13]:

$$n = Z^2_{(\alpha.\beta)} \frac{2s^2}{\Delta^2}$$

With parameters of (s = 8.76 , μg/mL), Δ= 7.6 μg/mL), (α = 0.05), (β = 0.1). This yielded a minimum sample size of 28 per group. We recruited 61 T2D patients and 40 controls.

Data Collection

Clinical information (age, sex, BMI, medical history) and laboratory results (1,5-AG, fasting plasma glucose, HbA1c, fructosamine) were collected. Blood samples were analyzed using the BECKMAN COULTER AU480 analyzer for glucose (ORS6121 kit, Beckman Coulter) and fructosamine (Biosystem S.A., Spain). The 1,5-AG levels were measured using the GlycoMark™ enzymatic assay (Tomen America, New York, NY). HbA1c was assessed via HPLC using the Premier Hb9210 system (Trinity Biotech, Ireland).

Statistical Analysis

Data were processed using SPSS 20.0, Excel 2007, and MedCalc 12.5. Continuous variables were expressed as mean ± standard deviation (SD). Differences between groups were assessed using t-tests or Mann-Whitney tests. ROC curves were used to evaluate diagnostic performance, with AUC values interpreted as: 0.6–0.7 (weak), 0.7–0.8 (moderate), 0.8–0.9 (good), >0.9 (excellent). Correlations between 1,5-AG and other biomarkers were analyzed using Pearson's correlation coefficient. A

p-value < 0.05 was considered statistically significant.

Ethical issues

The study was approved by the Biomedical Ethics Committee of Da Nang Hospital (No. 1030/BVDN-HDYD, August 27, 2019) and complied with the Declaration of Helsinki. Written informed consent was obtained from all participants.

RESULTS

Demographic and Clinical Characteristics

The T2D group comprised 33 males (54.1%) and 28 females (45.9%), with a mean age of 53.4 ± 7.0 years. The control group included 21 males (52.5%) and 19 females (47.5%), with a mean age of 53.2 ± 8.6 years (Table 1). The T2D group had a higher prevalence of overweight/obesity (60.7% vs. 32.5%) and a higher mean BMI (23.2 ± 0.9 vs. 22.2 ± 1.5, p < 0.05).

Table 1. *Demographic Characteristics of Study Participants*

Characteristic	T2D Group (n=61)	Control Group (n=40)	p-value
Sex, number (percentage)			*ns*
Male	33 (54.1)	21 (52.5)	
Female	28 (45.9)	19 (47.5)	
Age group, number (percentage)			*ns*
<60 years	51 (83.6)	31 (77.5)	
≥60 years	10 (16.4)	9 (22.5)	
Mean age (years, mean ± SD)	53.4 ± 7.0	53.2 ± 8.6	*ns*
BMI group, number (percentage)			<0.05
Normal	24 (39.3)	27 (67.5)	
Overweight/Obese	37 (60.7)	13 (32.5)	
Mean BMI (kg/m², mean ± SD)	23.2 ± 0.9	22.2 ± 1.5	<0.05

ns: not significant, SD: standard deviation

Glycemic Biomarkers

The T2D group exhibited significantly higher levels of HbA1c (7.2 ± 1.4% vs. 5.5 ± 0.2%), fasting glucose (7.3 ± 1.6 mmol/L vs. 4.8 ± 0.7 mmol/L), and fructosamine (336.4 ± 68.7 µmol/L vs. 254.8 ± 33.9 µmol/L) compared to controls (p < 0.01, Table 2).

Table 2. *Glycemic Biomarkers in Study Participants*

Biomarker	**T2D Group** (mean ± SD)	**Control Group** (mean ± SD)	p-value
HbA1c (%)	7.2 ± 1.4	5.5 ± 0.2	<0.01
Glucose (mmol/L)	7.3 ± 1.6	4.8 ± 0.7	<0.01
Fructosamine (µmol/L)	336.4 ± 68.7	254.8 ± 33.9	<0.01

Serum 1,5-AG Concentrations

The mean 1,5-AG concentration in T2D patients was 11.3 ± 8.0 µg/mL, significantly lower than in controls (27.2 ± 9.7 µg/mL, $p < 0.01$, Figure 1). No significant differences in 1,5-AG levels were observed between sexes or age groups within each cohort ($p > 0.05$, Tables 3 and 4).

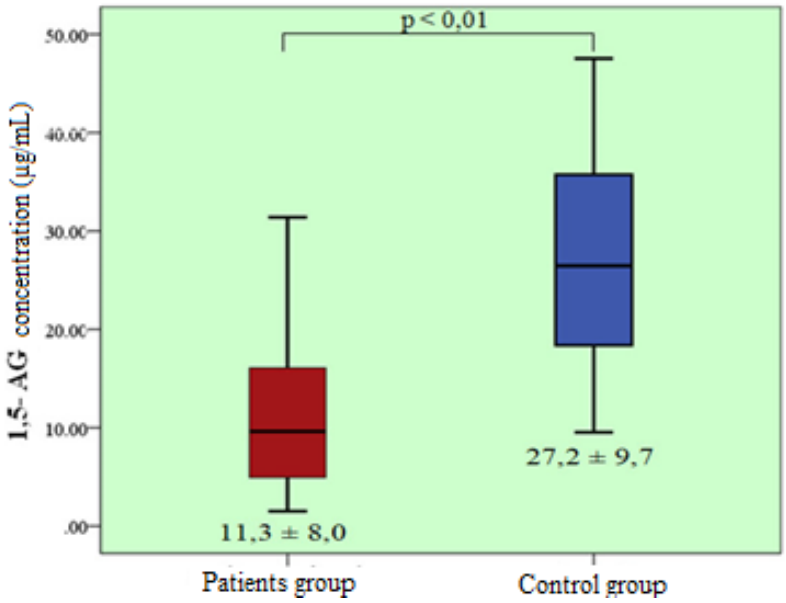

Figure 1. *Serum 1,5-AG Concentrations in T2D and Control Groups*

Mean 1,5-AG levels in T2D patients (11.3 ± 8.0 µg/mL) were significantly lower than in controls (27.2 ± 9.7 µg/mL, $p < 0.01$).

Table 3. *Serum 1,5-AG Concentrations by Sex and Age*

Category	**T2D Group** (µg/mL, mean ± SD)	**Control Group** (µg/mL, mean ± SD)	**p-value**
Sex			
Male	11.4 ± 7.7	29.0 ± 10.4	<0.01
Female	11.2 ± 8.4	25.3 ± 8.8	<0.01
p-value (within group)	ns	ns	
Age Group			
<60 years	11.0 ± 7.5	27.7 ± 10.4	<0.01
≥60 years	12.7 ± 10.3	25.8 ± 7.2	<0.01
p-value (within group)	ns	ns	

ns: not significant, SD: standard deviation

Diagnostic Performance of 1,5-AG

The ROC analysis demonstrated that 1,5-AG had good diagnostic performance for T2D, with an AUC of 0.897 (95% CI: 0.820–0.948, $p < 0.01$), sensitivity of 80.3%, specificity of 87.5%,

and a cutoff value of 17.0 µg/mL (Figure 2). Compared to other biomarkers, HbA1c (AUC = 0.980, sensitivity = 93.4%, specificity = 100%) and glucose (AUC = 0.944, sensitivity = 80.3%, specificity = 100%) showed excellent diagnostic performance, while fructosamine (AUC = 0.871, sensitivity = 68.9%, specificity = 95%) was comparable to 1,5-AG (Figure 3).

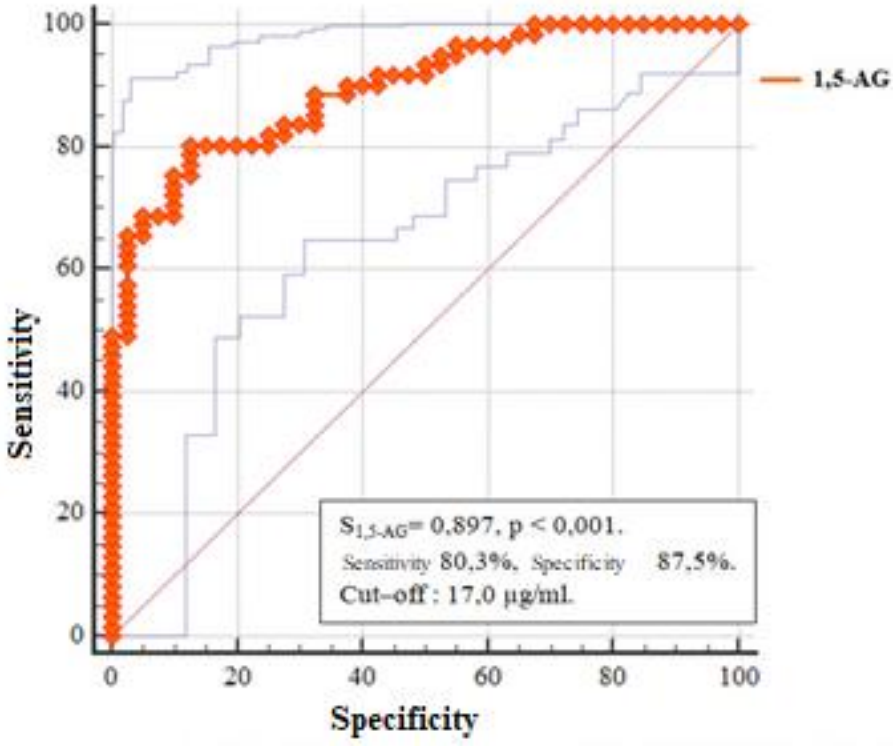

Figure 2. *ROC Curve for 1,5-AG in Diagnosing T2D*

The AUC for 1,5-AG was 0.897, with a sensitivity of 80.3% and specificity of 87.5% at a cut-off of 17.0 µg/mL.

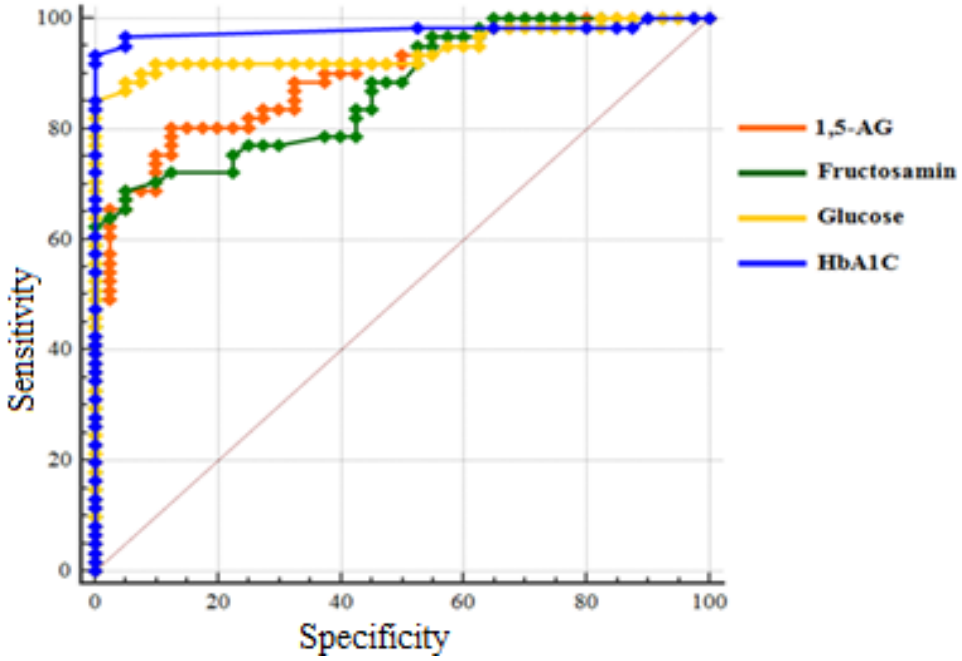

Figure 3. ROC Curves for 1,5-AG, HbA1c, Glucose, and Fructosamine

HbA1c (AUC = 0.980) and glucose (AUC = 0.944) outperformed 1,5-AG (AUC = 0.897) and fructosamine (AUC = 0.871) in diagnosing T2D.

Correlations with Other Biomarkers

Serum 1,5-AG showed significant negative correlations with HbA1c ($r = -0.512$, $p < 0.01$), fasting glucose ($r = -0.467$, $p < 0.01$), and fructosamine ($r = -0.489$, $p < 0.01$) in T2D patients. (Fig.3)

DISCUSSIONS

This study evaluated the diagnostic utility of serum 1,5-anhydroglucitol (1,5-AG) for type 2 diabetes mellitus (T2D) in a Vietnamese cohort, revealing significantly lower 1,5-AG levels in T2D patients (11.3 ± 8.0 µg/mL) compared to controls (27.2 ± 9.7 µg/mL, $p < 0.01$) [6]. The discussion below integrates our results with the Vietnamese context, focusing on demographic characteristics, 1,5-AG concentrations, and diagnostic performance.

Demographic and Clinical Characteristics

Unlike type 1 diabetes, which is more prevalent in females due to autoimmune mechanisms [14], T2D shows no clear gender predominance [11]. In our study, males comprised 54.1% (33/61) of the T2D group, slightly higher than females (45.9%, 28/61), consistent with local findings by Dao A.D. et al in Da Nang, where males accounted for 52.6% of T2D cases [15]. Variations in gender distribution across studies may stem from random sampling or regional differences in population sex ratios [2]. The mean age of T2D patients was 53.4 ± 7.0 years (range: 39–72 years), aligning with the typical age profile for T2D in Vietnam [16]. This age group is critical for targeted screening, as T2D prevalence increases with age due to insulin resistance and lifestyle factors [1].

Glycemic control remains a cornerstone of T2D management. Our study utilized fasting plasma glucose, HbA1c, and fructosamine to assess glycemic status, revealing significantly elevated levels in T2D patients compared to controls ($p < 0.01$): glucose (7.3 ± 1.6 mmol/L), HbA1c (7.2 ± 1.4%), and fructosamine (336.4 ± 68.7 µmol/L). These values exceed normal thresholds, indicating suboptimal glycemic control in the T2D cohort. Poor control underscores the need for stricter monitoring to prevent complications, such as cardiovascular disease and neuropathy, which are prevalent in Vietnamese T2D patients [17]. The higher prevalence of overweight/obesity in our T2D group (60.7% vs. 32.5% in controls, $p < 0.05$) further highlights the role of lifestyle interventions in Vietnam, where urbanization and dietary shifts contribute to rising obesity rates [18].

Serum 1,5-AG Concentrations

The mean 1,5-AG concentration in T2D patients was markedly lower than in controls, consistent with previous studies. For instance, Shirasaya et al. reported 11.76 ± 6.92 µg/mL in Japanese T2D patients [19], and Dworacka et al. found 10.2 ± 6.3 µg/mL in Polish patients [20]. Some studies reported even lower levels, such as Wang et al. (4.57 ± 3.71 µg/mL) and Lu et al. (4.02 ± 2.96 µg/mL) in Chinese cohorts [13, 21]. These variations may reflect differences in disease severity, treatment regimens, or assay methodologies.

The reduction in 1,5-AG levels in T2D is mechanistically linked to hyperglycemia. Normally, glucose is reabsorbed in the renal proximal tubules via sodium-glucose co-transporters (SGLT1 and SGLT2), while 1,5-AG is reabsorbed via SGLT4 [7]. In T2D, elevated urinary glucose competes with 1,5-AG for reabsorption, leading to increased 1,5-AG excretion and lower serum levels [8]. This makes 1,5-AG a sensitive marker of glycemic excursions, particularly in patients with normal renal function [9]. Our study found no significant sex-based differences in

1,5-AG levels within the T2D group (males: 11.4 ± 7.7 µg/mL; females: 11.2 ± 8.4 µg/mL, $p > 0.05$), consistent with published data [14]. However, in controls, male 1,5-AG levels (29.0 ± 10.4 µg/mL) were 1.15 times higher than female levels (25.3 ± 8.8 µg/mL), though this trend lacks consensus in the literature [10].

Diagnostic Performance of 1,5-AG

The ROC analysis demonstrated that 1,5-AG has good diagnostic performance for T2D, with an AUC of 0.897 (95% CI: 0.820–0.948, $p < 0.01$), sensitivity of 80.3%, specificity of 87.5%, and a cut-off of 17.0 µg/mL. These results are comparable to a Japanese study of 690 healthy individuals and 37 T2D patients, which reported an AUC of 0.89, sensitivity of 83.8%, specificity of 84.6%, and a cutoff of 17.1 µg/mL [19]. Similarly, Shah et al. found excellent diagnostic accuracy in U.S. adolescents with insulin resistance (AUC = 0.961, sensitivity = 96%, specificity = 88%, cut-off = 17.0 µg/mL) [22]. In Vietnam, 1,5-AG's diagnostic utility is particularly relevant given the high proportion of undiagnosed T2D cases (approximately 50% of cases nationwide) [23].

Compared to other biomarkers, HbA1c (AUC = 0.980, sensitivity = 93.4%, specificity = 100%) and fasting glucose (AUC = 0.944, sensitivity = 80.3%, specificity = 100%) outperformed 1,5-AG, while fructosamine (AUC = 0.871, sensitivity = 68.9%, specificity = 95%) was slightly less effective. However, 1,5-AG's simplicity, independence from fasting status, and sensitivity to postprandial glucose spikes make it ideal for community screening in Vietnam, where access to advanced diagnostics may be limited [24]. The diagnostic cutoff for 1,5-AG in Asian populations varies from 14.0 µg/mL (Japan) to 17.1 µg/mL [4,19]. Our cutoff of 17.0 µg/mL aligns with international data but may reflect population-specific factors, such as ethnicity or sample size [25].

In Vietnam, where T2D prevalence is rising due to urbanization and lifestyle changes [26], 1,5-AG offers a practical tool for early detection. Its non-reliance on fasting or meal timing simplifies testing in resource-constrained settings, such as rural clinics [27]. However, community-based screening with 1,5-AG may yield lower sensitivity and specificity compared to high-risk group screening, as noted in Asian studies [4]. Future research should validate 1,5-AG cutoffs in larger, multi-center Vietnamese cohorts and explore its cost-effectiveness for national screening programs.

This study's limitations include its small sample size (61 T2D patients, 40 controls) and single-center design, which may limit generalizability to Vietnam's diverse population. Additionally, we did not assess postprandial glucose levels, which could provide further insights into 1,5-AG's sensitivity to glycemic excursions. Future studies should address these gaps and investigate 1,5-AG's role in monitoring treatment response and predicting complications.

CONCLUSIONS

To conclude, serum 1,5-AG is a reliable biomarker for diagnosing T2D in Vietnamese patients, offering good diagnostic performance with a cutoff of 17.0 µg/mL. Its ability to reflect short-term glycemic control complements conventional markers like HbA1c and glucose. Incorporating 1,5-AG into clinical practice could enhance T2D diagnosis and management, particularly for detecting early glycemic excursions.

Supplementary Materials

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Author Contributions

Study concept and design: TTL; data acquisition: LTN; data analysis and interpretation: TTL, LTN; manuscript drafting: TTL, LTN; statistical analysis: LTN; manuscript revising: TTL.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Biomedical Ethics Committee of Da Nang Hospital (No. 1030/BVDN-HDYD, August 27, 2019).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

Data supporting the reported results are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflict of interest.

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