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Evaluation of 1,5-Anhydroglucitol, Hemoglobin A1c, and Glucose Levels in Youth and Young Adults with Type 1 Diabetes and Healthy Controls

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Abstract

Background and objective—Serum 1,5-anhydroglucitol (1,5-AG) is a marker of hyperglycemic excursions in adults with diabetes and HbA1c <8%. We compared 1,5-AG levels among youth and young adults with and without type 1 diabetes (T1D) and investigated the utility of 1,5-AG in the assessment of glycemic status in pediatric T1D.

Methods—We compared 1,5-AG, HbA1c, and plasma glucose levels in 138 patients with T1D (duration 1 year) and 136 healthy controls, ages 10–30 years. Within each group, we investigated associations between 1,5-AG and clinical characteristics, HbA1c and random plasma glucose. For patients with T1D, 1,5-AG was further analyzed according to HbA1c strata: <8%, 8–9%, and >9%.

Results—Compared to controls, patients with T1D had higher HbA1c ($8.5 \pm 1.6\%$ vs. $5.1 \pm 0.4\%$, $p < 0.0001$), lower 1,5-AG (4.0 ± 2.0 vs. 24.7 ± 6.4 $\mu\text{g/mL}$, $p < 0.0001$), and higher glucose (11.1 ± 5.2 vs. 5.1 ± 0.9 mmol/L, $p < 0.0001$). Males had higher 1,5-AG than females within patients (4.5 ± 2.3 vs. 3.4 ± 1.6 $\mu\text{g/mL}$, $p = 0.003$) and controls (26.0 ± 6.6 vs. 23.5 ± 6.0 $\mu\text{g/mL}$, $p = 0.02$). 1,5-AG was not correlated with glucose in either group. 1,5-AG was significantly correlated to HbA1c in patients, but not controls. For patients with HbA1c <8%, 1,5-AG demonstrated the widest range and was not predicted by HbA1c; 1,5-AG levels were narrowly distributed among patients with HbA1c 8%.

Conclusions—Youth and young adults with T1D demonstrate similar 1,5-AG levels which are distinct from controls. 1,5-AG assessment may provide unique information beyond that provided by HbA1c in the mid-term assessment of glycemic control in young patients with T1D and HbA1c <8%.

Keywords

Diabetes mellitus; type 1; Pediatrics; Hemoglobin A; glycosylated; 1,5-anhydroglucitol

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INTRODUCTION

The Diabetes Control and Complications Trial (DCCT) demonstrated that near normal glycemic control, assessed by HbA1c, significantly reduced the risk of long-term complications for individuals with type 1 diabetes (T1D).[1] Intensive insulin therapy aimed at lowering HbA1c levels is the standard of care for this population. Subsequent analyses of the DCCT cohort concluded that over 95% of the glycemic impact on long-term complications was related to HbA1c levels.[2,3] The additional role of postprandial glucose and glycemic variability in complication risk has been suggested in T1D, but remains an active area of investigation.[4]

HbA1c levels measure average glycemia over the preceding 8–12 weeks and cannot assess daily glycemic excursions.[5] Daily self-monitoring of blood glucose (SMBG) is required for timely detection and management of acute glycemic excursions. Continuous glucose monitoring (CGM) studies demonstrate that SMBG may not capture the frequency, magnitude, and duration of glycemic excursions in youth with type 1 diabetes.[6] While CGM may become the “gold-standard” for detecting and managing glycemic excursions in the future, technical, financial and psychological issues have limited widespread adoption to date.[7]

A short-term glycemic marker sensitive to glycemic excursions could provide unique and valuable feedback following therapeutic and dietary interventions in T1D before changes in HbA1c are evident. Glycated proteins, such as fructosamine, provide short-term (2–3 week) measures of average glycemia and are unlikely to provide information beyond mean blood glucose calculated from SMBG over the same interval.[5] In 2003, 1,5-anhydroglucitol (1,5-AG), a naturally-occurring monosaccharide that is structurally similar to glucose, was approved as a laboratory marker of short-term glycemic excursions.[8,9] Normally, 1,5-AG is freely filtered in the kidneys with 99.9% reabsorption by renal tubules. Urinary excretion of 1,5-AG is matched by dietary intake, the primary source of 1,5-AG, resulting in stable serum concentrations.

For non-pregnant individuals without diabetes, kidney or liver disease, 1,5-AG levels are stable.[10,11] However, when serum glucose levels exceed the renal threshold for reabsorption, glucose competitively inhibits 1,5-AG reabsorption leading to urinary excretion of 1,5-AG and lower serum concentrations.[12] As such, adults with diabetes have significantly lower 1,5-AG levels compared to the general population.[13]

The metabolism, quantification and clinical utility of 1,5-AG has been reviewed extensively in adults with and without diabetes.[12,14,15] To date, there is limited information regarding the utility of 1,5-AG in youth with T1D, and additional studies have been recommended.[15,16] The aim of the current study is to examine the performance of 1,5-AG in a large sample of youth and young adults with and without T1D.

METHODS

We analyzed previously collected cross-sectional data and laboratory samples. Patients with T1D (n=138) were recruited from the Joslin Diabetes Center (Boston, MA) following regularly scheduled clinic visits. Participants without diabetes (n=136) were recruited from online classified ads, local primary care physicians or a nearby pre-operative clinic. Patients with T1D had diabetes duration ≥ 1 year, and controls had no family history of diabetes among first-degree relatives. Both patients and controls were 10–30 years old, did not have chronic kidney disease, and were not pregnant. Following local Institutional Review Board approval, written informed consent was obtained from participants aged ≥ 18 years and guardians of youth <18 years, and assent was obtained from youth <18 years.

Demographic and clinical information were collected. Overweight was defined as age- and sex-adjusted BMI 85th percentile and <95th percentile for participants 20 years old or a BMI from 25 to <30 kg/m² for participants >20 years old; obesity was defined as age- and sex-adjusted BMI 95th percentile for participants 20 years old or a BMI 30 kg/m² for participants >20 years old. Pubertal status was not assessed.

Participants had a non-fasting, venous blood draw during a one-time study visit; blood was collected in EDTA purple top tube (HbA1c), grey top tube (plasma glucose) and serum-separating tube (serum creatinine). HbA1c (Tosoh A1c 2.2 Plus Glycohemoglobin Analyzer™, Tosoh Bioscience, Inc., South San Francisco, CA) was assayed using high-performance liquid chromatography with reference range 4.0–6.0%. Plasma glucose (Ortho-Clinical Diagnostics, Inc., Rochester, NY) and 1,5-AG (GlycoMark™, GlycoMark, Inc., Winston-Salem, NC) were measured using an enzymatic colorimetric assay. Reference ranges for 1,5-AG were 6.8–29.3 µg/mL for females and 10.7–32.0 µg/mL for males. Serum creatinine (Beckman CX9 Chemistry Analyzer, Beckman Coulter, Inc., Brea, CA) was measured using Jaffe methodology with reference range 0.4–1.3 mg/dL. Venous blood samples were analyzed immediately for HbA1c, plasma glucose and serum creatinine; unused serum was aliquoted and stored at –80°C in 1.5-mL polypropylene vials and used for 1,5-AG assessment. 1,5-AG stability under these conditions has been validated.[14]

Descriptive statistics are presented as means ± SD (range) or percentages. Student's *t* test and chi-square analyses were used to determine differences in means and proportions between groups, respectively. 1,5-AG levels were compared between youth (<18 years) and young adults (>18 years) within and between both groups. Correlations compared 1,5-AG levels to other continuous variables, including HbA1c and plasma glucose. Multivariate regression analyses predicted 1,5-AG among patients with T1D grouped according to HbA1c strata (<8%, 8–9%, and >9%). Variance in 1,5-AG among these groups was compared using the F test. Two-sided *p* values <0.05 indicated statistical significance. Statistical analyses were performed using Statistical Application Software (version 9.2; SAS Institute, Inc., Cary, NC).

RESULTS

Study population

Demographic and clinical characteristics of patients with T1D (n=138) and controls (n=136) are summarized in Table 1. Patients were older and less racially diverse compared to controls. Youth <18 years comprised 38% (n=52) of patients with T1D and 63% (n=85) of controls. As expected, HbA1c and non-fasting plasma glucose levels were significantly higher in patients with T1D compared to controls. Participants with chronic kidney disease were excluded from participation and a majority of patients (70%) and controls (55%) had serum creatinine levels. Serum creatinine levels were not significantly different between patients and controls.

Patients with T1D received intensive therapy (48% insulin pump therapy and 52% multiple daily injections [MDI]) and had a mean diabetes duration of 14.6 ± 4.5 years. Mean HbA1c was 8.5±1.6% (range 5.8–17.5%); HbA1c was significantly associated with treatment regimen (pump: 8.2±1.0% vs. MDI: 8.7±2.0%, *p*=0.04) and modestly correlated with daily insulin dose (*r*=0.19, *p*=0.04).

Levels of 1,5-AG in patients and controls

The distribution of 1,5-AG among patients and controls are presented in Fig. 1. Values were normally distributed among controls, but skewed to the right among patients due to floor effects. Patients with T1D had significantly lower 1,5-AG compared to controls (4.0 ± 2.0

vs. 24.7 ± 6.4 , $p < 0.0001$). In the control group, 82% ($n=111$) had 1,5-AG levels in the reference range with the remaining 17% ($n=23$) above and 1% ($n=2$) below the reference range. The majority of controls with 1,5-AG levels above the reference range were <20 years old. Conversely, in the patient group, 97% ($n=134$) had 1,5-AG values below the reference range with only 3% ($n=4$) within the reference range, and none above. 1,5-AG was not associated with serum creatinine in controls. 1,5-AG was correlated with serum creatinine in patients with T1D. However, after controlling for HbA1c and sex, 1,5-AG was not significantly associated with serum creatinine in patients with T1D.

The associations between 1,5-AG and demographic and clinical parameters are presented in Table 2. Youth with T1D ≤ 18 years had significantly lower 1,5-AG levels compared to control subjects ≤ 18 years (4.2 ± 2.1 vs. 25.9 ± 5.7 , $p < 0.0001$). Similarly, young adults with T1D >18 years had significantly lower 1,5-AG levels compared to control subjects >18 years (3.8 ± 2.0 vs. 22.5 ± 6.9 , $p < 0.0001$). Within patients with T1D, 1,5-AG levels were not significantly different between youth ≤ 18 years and young adults >18 years (4.2 ± 2.1 vs. 3.8 ± 2.0 , $p=0.3$). However, within control subjects, youth ≤ 18 years had significantly higher 1,5-AG levels compared to young adults >18 years (25.9 ± 5.7 vs. 22.5 ± 6.9 , $p=0.004$). 1,5-AG was inversely correlated with age in controls, but not in patients with T1D. Within controls, age remained significantly associated with 1,5-AG after controlling for sex and HbA1c.

Within patient and control groups, males had significantly higher 1,5-AG compared to females; this sex difference remained significant after controlling for age and HbA1c. There was borderline significance ($p=0.05$) in the difference between 1,5-AG levels in patients using CSII compared to those using MDI. This trend for differences in 1,5-AG levels in CSII- vs. MDI-treated patients resulted from the lower HbA1c in the former group. After adjusting for HbA1c, 1,5-AG levels were not different between these two groups ($p=0.3$).

Glycemic marker associations

The 1,5 AG levels in both patients with T1D and controls demonstrated a non-linear relationship with HbA1c with an apparent HbA1c breakpoint of 6% (Fig. 2). The 1,5-AG levels displayed substantial variation ($8.9\text{--}44.5$ $\mu\text{g/mL}$) among the non-diabetic controls with $\text{HbA1c} < 6\%$. In patients with type 1 diabetes, the 1,5-AG levels demonstrated a significant inverse correlation with HbA1c ($r=-0.53$, $p < 0.0001$), likely due to the wide range in HbA1c values ($5.8\text{--}17.5\%$). In the controls, 1,5 AG and A1c values were not correlated ($r=-0.04$, $p=0.6$). Random plasma glucose was not associated with HbA1c nor was it associated with 1,5-AG in either group.

Finally, we assessed 1,5-AG levels in patients according to HbA1c strata: $<8\%$, $8\text{--}9\%$ and $>9\%$. For $\text{HbA1c} < 8\%$, 1,5-AG was not significantly correlated with HbA1c ($r=-0.17$, $p=0.2$). However, 1,5-AG and HbA1c were significantly correlated when HbA1c values were between $8\text{--}9\%$ ($r=-0.41$, $p=0.004$). Again, there was no correlation when HbA1c was $>9\%$ ($r=-0.28$, $p=0.1$). The range of 1,5-AG values was significantly greater for those either with $\text{HbA1c} < 8\%$ ($1.5\text{--}11.1$ $\mu\text{g/mL}$) compared to patients with HbA1c between $8\text{--}9\%$ ($1.5\text{--}6.9$ $\mu\text{g/mL}$) ($F=3.3$, $p < 0.0001$) or $\text{HbA1c} > 9\%$ ($1.0\text{--}8.7$ $\mu\text{g/mL}$) ($F=2.71$, $p=0.002$). There was no significant difference in the range of 1,5-AG values between those with HbA1c between $8\text{--}9\%$ and $\text{HbA1c} > 9\%$ ($F=1.22$, $p=0.5$).

DISCUSSION

We investigated the performance of 1,5-AG in a cohort of youth and young adults with and without T1D. There was little overlap between 1,5-AG levels in patients with T1D and controls, with patients having significantly lower, subnormal values compared to controls. In

controls, subrenal threshold glucose concentrations likely allowed for 1,5-AG renal reabsorption avoiding urinary 1,5-AG losses.[12] 1,5-AG levels were likely lower in patients with T1D due to more frequent hyperglycemic excursions exceeding the renal threshold for glucose, limiting opportunities for recovery of filtered 1,5-AG levels.[17] In a subsample of youth and young adults with available serum creatinine values, serum creatinine was not associated with 1,5-AG after adjustment for sex and HbA1c. 1,5-AG levels among youth and young adults with T1D appear similar to adults with diabetes, which are below the reference range for individuals without diabetes.

We compared 1,5-AG to established glycemic markers, HbA1c and plasma glucose, in youth and young adults with T1D. Although 1,5-AG levels were not associated with a single, random plasma glucose value, studies have demonstrated associations from average glucose levels derived more frequent sampling suggesting less dynamic fluctuations in 1,5-AG concentrations compared to glucose concentrations. Our demonstration that 1,5-AG was inversely correlated with HbA1c is consistent with studies in adults with T1D and T2D.[15] A previously published study of 10 youth with and 10 youth without diabetes reported a strong correlation between 1,5-AG and HbA1c. However, their finding can be explained as an artifact of combining both patient and control values.[16] If we combined our patient and control values, then the correlation between 1,5-AG and HbA1c would -0.78 ($p < 0.0001$), but we believe this higher correlation results from anchoring the extreme values from patient and control groups and is not clinically relevant.

Studies of adults with diabetes suggest that 1,5-AG may contribute unique information regarding glycemia and glycemic excursions at levels of HbA1c less than 8%. [9,15,18] We studied youth and young adults with T1D grouped according to HbA1c level: $<8\%$, $8-9\%$, and $>9\%$. In patients with HbA1c $<8\%$, 1,5-AG values varied significantly and were independent of HbA1c suggesting that 1,5-AG may provide unique information regarding glycemia in youth with diabetes. For example, a patient with HbA1c $<8\%$ and low 1,5-AG may be experiencing more frequent postprandial hyperglycemia alternating with hypoglycemia than a patient with HbA1c $<8\%$ and higher 1,5-AG levels. Serum 1,5-AG levels decline significantly following episodes of hyperglycemia, but there is no data to suggest that hypoglycemia would permit supraphysiologic levels. As such, individuals with T1D with near-normal HbA1c and low 1,5-AG levels may be experiencing larger fluctuations in blood glucose with greater risk of hypoglycemia. In fact, the presence of undetected nocturnal hypoglycemia is common in patients with lower HbA1c.[19] Thus, a clinically relevant application for the use of 1,5-AG may be in patients with HbA1c $<8\%$ in order to identify those at greater risk for hypoglycemic events. Future studies comparing 1,5-AG levels to continuous glucose monitoring data will help clarify the relationship between 1,5-AG and glycemic variability. Alternatively, for patients with HbA1c $\geq 8\%$, the limited range of 1,5-AG values is likely due to the presence of chronic hyperglycemia preventing recovery of 1,5-AG, leading to urinary depletion.[17] A clinically relevant application for youth with HbA1c $\geq 8\%$ may be to detect serial increases of 1,5-AG values prior to any observed changes in HbA1c following therapeutic changes.[20]

In our cohort of youth with established with T1D, we found no association between 1,5-AG and age, race, weight status or diabetes duration. Prior studies have reported 1,5-AG levels to be in the reference range for youth and adults with obesity or prediabetes.[21,22] Interestingly, many of our young subjects without diabetes demonstrated 1,5-AG levels above the reference range. This finding along with the significant, inverse correlation of age with 1,5-AG in our control subjects suggests the need for additional studies in young populations. Age-specific differences in 1,5-AG levels may relate to changes in renal threshold for glucosuria which varies with age in the absence of diabetes or underlying kidney disease.[24,25] We also demonstrated significantly higher levels of 1,5-AG in males

compared to females in both patient and control populations. This is consistent with prior studies, including the validation study for the GlycoMark™ assay [14]. However, in a single, large, international study of adults with T2D, 1,5-AG levels were found to be significantly higher in women despite their higher HbA1c without explanation for the exception.[23] Sex-specific and regional variations in 1,5-AG intake or metabolism may help explain these findings and warrant further investigation. Age- and sex-specific differences in 1,5-AG levels in youth may relate to differences in pubertal timing and status, a period of relative insulin resistance. Pubertal status was not assessed in this study and remains another area for further investigation. 1,5-AG levels may also be higher in certain racial and ethnic populations, namely persons of Asian or African descent.[15,18,23] The racial and ethnic differences were not explained by HbA1c and may be related to other factors, including dietary patterns. The lack of racial differences in 1,5-AG levels in our sample may be result from the limited numbers of minority participants. Additional limitations of this study includes its cross-sectional study design and the absence of continuous glucose monitoring data to understand the association between of glycemic excursions and 1,5-AG levels.

1,5-AG appears to be a short-term indicator of glycemic excursions in individuals with T1D. Unlike HbA1c, multiple factors may limit the comparison of 1,5-AG levels between individuals. The utility of 1,5-AG levels may lie in serial measurements within an individual to assess recent changes in glycemia. Longitudinal studies of youth and young adults with T1D will clarify its potential role in the management of this population. 1,5-AG levels have not been associated with the risk of acute or chronic diabetes complications and should be considered supplemental to both HbA1c and SMBG in the management of T1D.[15]

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Figure 1.
Distribution of 1,5-AG levels in patients with T1D (white) and controls (black).

Figure 2.

Serum 1,5-AG levels according to HbA1c in patients with T1D and controls. 1,5-AG ranged from 1.5–11.1 µg/mL in patients with HbA1c <8% (white triangles), 1.5–6.9 µg/mL in patients with HbA1c 8–9% (gray squares), 1.0–8.7 µg/mL for patients with HbA1c >9% (white circles) and 8.9–44.5 µg/mL in controls (black diamonds).

Table 1

Characteristics of participants with and without type 1 diabetes (N=274)

	Patients (n=138)	Controls (n=136)	<i>p</i> value
Age (years)	20.4 ± 5.2 (10.6–30.5)	17.8 ± 5.5 (10.0–29.9)	0.0001
Sex (% female)	51	54	0.5
Race (% white)	94	76	<0.0001
Creatinine (mg/dL) *	0.9 ± 0.2 (0.5–1.3)	0.9 ± 0.2 (0.4–1.7)	0.8
HbA1c (%)	8.5 ± 1.6 (5.8–17.5)	5.1 ± 0.4 (4.3–6.0)	<0.0001
Glucose, random (mmol/L)	11.1 ± 5.2 (1.6–28.3)	5.1 ± 0.9 (3.1–7.8)	<0.0001
1,5-AG (µg/mL)	4.0 ± 2.0 (1.0–11.1)	24.7 ± 6.4 (8.9–44.5)	<0.0001
Weight status (%)			0.001
Not overweight	53	75	
Overweight	36	16	
Obese	12	9	
Diabetes duration (years)	14.6 ± 4.5 (4.4–28.7)		
Insulin regimen (%)			
3 injections/day	20		
4+ injections/day	32		
Insulin pump	48		
Insulin dose (units/kg/day)	0.8 ± 0.2 (0.3–1.4)		

* Subsample of patients (n=96) and controls (n=75)

Table 2

Relationship of clinical and laboratory characteristics to 1,5-AG among patients with T1D and controls

Characteristic	Patients (n=138)		Controls (n=136)	
	Relationship to 1,5-AG*	p value	Relationship to 1,5-AG*	p value
Age (years)	-0.06	0.5	-0.29	0.0007
Sex		0.003		0.02
Male	4.5 ± 2.3 (1.1–11.1)		26.0 ± 6.6 (10.3–44.5)	
Female	3.4 ± 1.6 (1.0–8.5)		23.5 ± 6.0 (8.9–37.3)	
Race		0.6		0.6
White	3.9 ± 2.0 (1.0–11.1)		24.8 ± 6.3 (8.9–44.5)	
Non-white	4.4 ± 2.3 (1.6–8.7)		24.1 ± 6.8 (10.6–37.3)	
Weight status		0.2		0.3
Not overweight	3.6 ± 1.9 (1.1–10.2)		24.0 ± 6.8 (8.9–44.5)	
Overweight	4.3 ± 2.1 (1.0–11.1)		24.1 ± 6.9 (12.8–37.3)	
Obese	4.3 ± 2.4 (1.5–10.0)		27.3 ± 6.7 (15.8–37.6)	
HbA _{1c} (%)	-0.53	<0.0001	-0.04	0.6
Glucose (mmol/L)	-0.13	0.2	0.05	0.7
Insulin regimen		0.05		
Pump	4.3 ± 2.0 (1.1–10.0)			
Injections	3.6 ± 2.0 (1.0–11.1)			

* Comparisons within patient and control groups presented as means ± SD (range) of 1,5-AG (µg/mL) for categorical variables or correlations with 1,5-AG for continuous variables.