

Original Article

Serum 1,5-anhydroglucitol (Glycomark™) levels in children with and without type 1 diabetes mellitus

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Abstract: Postprandial hyperglycemia associated with diabetes is a risk factor for cardiovascular disease. Currently, glycated hemoglobin A_{1c} (HgbA_{1c}) and glycated protein fructosamine are not sensitive markers for acute and short-term hyperglycemia. 1,5-Anhydroglucitol (1,5-AG) (Glycomark™; Tomen America, New York, NY, USA) is reported in adults with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) as a marker for postmeal hyperglycemia. However, the reference ranges for 1,5-AG in normal children and children with T1DM are not known. We studied 1,5-AG levels in 10 control children (6 males and 4 females) and 10 children with T1DM (7 males and 3 females). The levels of 1,5-AG in the normal controls were higher than those in children with T1DM ($24.60 \pm 3.99 \mu\text{g/mL}$ vs. $4.75 \pm 2.95 \mu\text{g/mL}$; $p < 0.0001$). There were no gender differences noted. The 1,5-AG levels were negatively correlated with HgbA_{1c} ($r = -0.9366$; $p < 0.0001$) and the peak postmeal plasma glucose concentrations (Pearson $r = -0.7230$; $p = 0.0003$). Our findings suggest that despite good glycemic control, postprandial glucose concentrations are elevated and that 1,5-AG showed a difference between controls and children with T1DM. The data are comparable with previous studies in normal adults and in those with T1DM and T2DM. They support the use of 1,5-AG concentrations, together with HgbA_{1c}, to evaluate therapy, especially to target postprandial hyperglycemia.

**Thanh M Nguyen,
Luisa M Rodriguez,
Kimberly J Mason and
Rubina A Heptulla**

Department of Pediatrics, Division of Endocrinology & Metabolism, Baylor College of Medicine and Texas Children's Hospital, Houston, TX, USA

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Corresponding author:
Rubina A Heptulla
Clinical Care Center, Suite 1020
6621 Fannin Street CC 1020.05
Houston
TX 77030-2399
USA.
Tel: 832 822 3779;
fax: 832 825 3673;
e-mail: heptulla@bcm.tmc.edu

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Mounting evidence suggests that postprandial hyperglycemia is an independent risk factor for cardiovascular diseases in patients with type 2 diabetes mellitus (T2DM) (1, 2). Postprandial hyperglycemia occurs even in well-controlled patients with diabetes. In one study, adults with type 1 diabetes mellitus (T1DM) and T2DM had an overall postmeal maximum glucose of 204 mg/dL and mean glycated hemoglobin A_{1c} (HgbA_{1c}) of 7.2% (3). In another study, despite good glycemic control (HgbA_{1c} of 7.7%), almost 90% of the children with T1DM had postprandial hyperglycemia greater than 180 mg/dL and half of them had postmeal glucose concentrations more than 300 mg/dL (4). The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus trial showed that the α -glucosidase inhibitor, acarbose, which specifically targets post-

prandial hyperglycemia, reduced the risk of developing T2DM, hypertension, and cardiovascular events by 25, 34, and 49%, respectively (5). These findings suggest the importance of improving postprandial hyperglycemia.

The first and foremost step to achieving optimal after-meal glucose concentrations is to have benchmarks for monitoring. Currently, there are two available glycemic markers: glycated protein fructosamine (FA) and HgbA_{1c}. FA correlates directly with and reflects the average serum glucose concentrations in the past 2–3 wk (6). The gold standard glycemic marker HgbA_{1c} correlates directly with and reflects the average serum glucose concentrations in the past 2–3 months (6). However, these two markers fail to detect worsening hyperglycemia in a 2-wk period (7).

Hence, there is a clear need for a marker to detect short-term hyperglycemia.

The 1-deoxy form of glucose known as 1,5-anhydroglucitol (1,5-AG) is proposed as a marker to evaluate postprandial glycaemic control in T1DM (8) and T2DM (7, 9). 1,5-AG reflects the overall glycaemic control between 1 d and a week (6). More importantly, 1,5-AG is a sensitive marker of elevated after-meal glucose concentration in adults with T1DM and T2DM (3, 10). Furthermore, studies in Japan and the USA showed that serum 1,5-AG levels correlated well with longitudinal changes in blood glucose in adult patients with T1DM and T2DM (3, 7, 11, 12).

1,5-AG was discovered in plants and humans in 1888 and 1972, respectively (6). The physiologic role of 1,5-AG in humans is currently not known. The normal serum concentration of 1,5-AG has been reported as 12–40 $\mu\text{g/mL}$ (13). The stable pool of 500–1000 mg of 1,5-AG is maintained by food intake at 4.38 mg/d, *de novo* synthesis at 0.4 mg/d, and excretion in the urine without being metabolized at 4.76 mg/d (14). It is reported that 99.9% of the filtered 1,5-AG in the renal tubules is reabsorbed, and the renal reabsorption is competitively inhibited by glucose (13). In patients with diabetes, glucosuria inhibits the reabsorption of 1,5-AG in the renal tubule and thus lowers the serum level of 1,5-AG. However, there are no published data on the 1,5-AG serum concentrations in normal children or in children with T1DM. In this communication, we report the 1,5-AG levels in a small cohort of adolescents with T1DM.

Methods

The institutional review board of the Baylor College of Medicine approved this study, which was a part of a study published previously (15). Briefly, eighteen 12- to 18-yr-old subjects with T1DM on insulin pump therapy and 12 age- and sex-matched control subjects were screened. Inclusion criteria were body mass index of < 90th percentile for age, hemoglobin ≥ 12 g/dL, hemoglobin A_{1c} $\leq 8\%$, no other chronic conditions besides diabetes and/or hypothyroidism, and no medications affecting glucose concentration. Eleven subjects with T1DM (7 males and 4 females) and eleven control subjects (6 males and 5 females) were qualified for the study. In this report, data are reported on 10 controls and 10 subjects with T1DM because of inadequacy of samples in two subjects. The HgbA_{1c} was performed at screening visit for each subject, except one male with T1DM and one female control. 1,5-AG levels and postprandial peak glucose concentrations were drawn during the time the patients underwent baseline evaluation of their plasma glucose fluctuation after a standard 12 oz liquid mix meal with 360 calories, 50 g carbohydrates, and 22 g of protein. 1,5-AG levels were drawn 60 min after the mixed meal

was ingested. Blood HgbA_{1c} was measured using a DCA 2000 HgbA_{1c} system (Bayer, Elkhart, IN, USA), with detection range between 2 and 14%. The plasma glucose concentrations were measured using the glucose analyzer (2300 Stat Plus; Yellow Springs Instrument, Yellow Springs, OH, USA). The samples were sent to Esoterix (Austin, TX, USA) for plasma 1,5-AG levels, using an enzymatic colorimetric Glycomark™ assay (Tomen America, New York, NY). According to the package insert, the Glycomark™ assay has a linear detection range of 0–113 $\mu\text{g/mL}$, intraassay variation of 1.3–3.8%, and interassay variation of 1–4% based on a US study (16).

Statistical analysis

Statistical analyses were performed using the Prism 4 for Windows by GraphPad Software, Inc. (San Diego, CA, USA). The two-tail, unpaired *t*-test was used to compare the 1,5-AG levels, HgbA_{1c}, or peak glucose concentrations between the two groups: normal vs. children with T1DM. The two-tailed Pearson test was used to determine the correlation between 1,5-AG levels and the peak glucose concentrations or HgbA_{1c}. The results were expressed as mean \pm SD. Significance was considered at <0.05. The figures were also generated from the same software program.

Results

The level of HgbA_{1c} was significantly different between the children without and with T1DM ($4.99 \pm 0.35\%$ vs. $7.72 \pm 0.37\%$; $p < 0.0001$) (Fig. 1A). The levels of 1,5-AG in the normal children were higher than those in children with T1DM (24.60 ± 3.99 $\mu\text{g/mL}$ vs. 4.75 ± 2.95 $\mu\text{g/mL}$; $p < 0.0001$) (Fig. 1B). There was no difference in the 1,5-AG levels between the male and female sex for the normal children (male: 24.57 ± 5.01 $\mu\text{g/mL}$ vs. female: 24.65 ± 2.44 $\mu\text{g/mL}$; $p = 0.98$) and for children with T1DM (male: 4.56 ± 3.21 $\mu\text{g/mL}$ vs. female: 5.20 ± 2.80 $\mu\text{g/mL}$; $p = 0.77$). The peak plasma glucose levels were lower in the normal children in comparison with those in children with T1DM (125 ± 17 mg/dL vs. 194 ± 41 mg/dL; $p < 0.0001$) (Fig. 1C). The 1,5-AG levels were negatively correlated with the HgbA_{1c} (Pearson $r = -0.9366$; $p < 0.0001$) (Fig. 2A) and the peak plasma glucose (Pearson $r = -0.7230$; $p = 0.0003$) concentrations (Fig. 2B).

Discussion

In this study, we report the value of 1,5-AG in children with and without T1DM. In normal children, the 1,5-AG levels range from 15.6 to 29.2 $\mu\text{g/mL}$. There was no difference in the 1,5-AG levels between the male and the female children, likely because of the small samples. Although the normal range of 1,5-AG

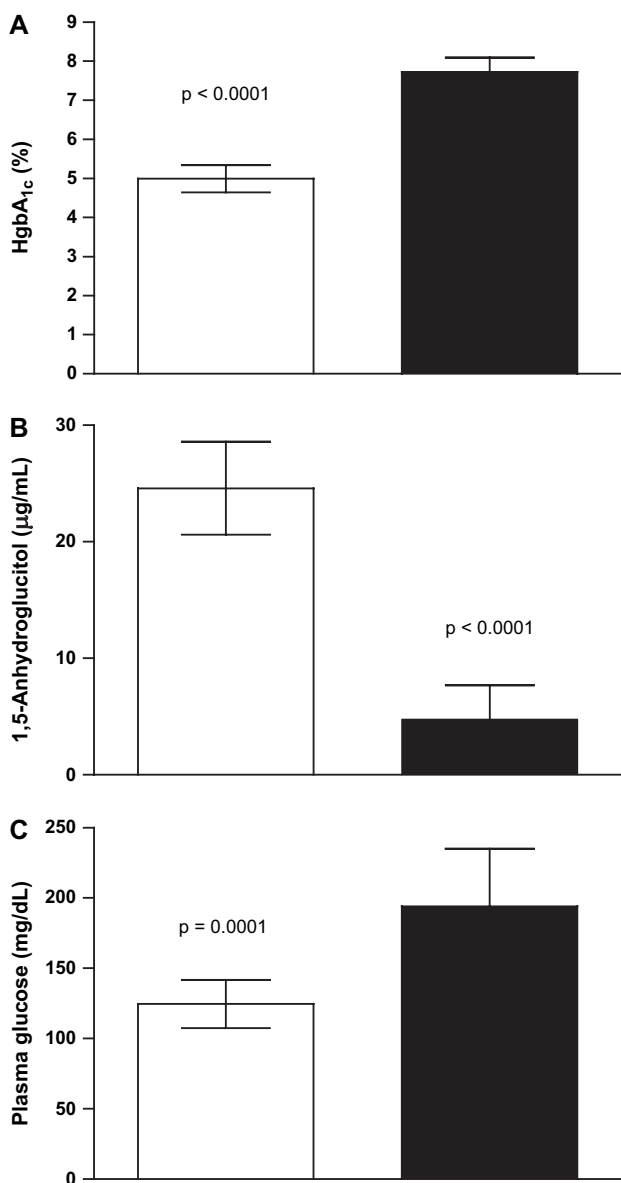


Fig. 1. (A) HgbA_{1c}, (B) 1,5-anhydroglucitol, and (C) peak glucose concentrations in normal children (open bar) and in children with T1DM (filled bar). HgbA_{1c}, glycated hemoglobin A_{1c}; T1DM, type 1 diabetes mellitus.

levels for children prior to our study was not established, the normal range of the 1,5-AG levels for normal adults is reported in Japanese and American studies (Table 1). For instance, the Glyco-mark™ assay offered for adults has a non-parametric 2.5th–97.5th reference interval of 10.2–33.8 µg/mL for men and 5.9–31.8 µg/mL for women (16). This was established by a US study of 224 normal adults aged 18 yr and older. The sample included African Americans, Caucasians, Asians (South Pacific), and Hispanics, with equal representation of both genders. Yamanouchi et al. reported various reference ranges for the normal individuals in Japan as 9.6–38.8 µg/mL (n = 45) in 1987 (17) and 13.4–28.3 µg/mL (n = 200) in

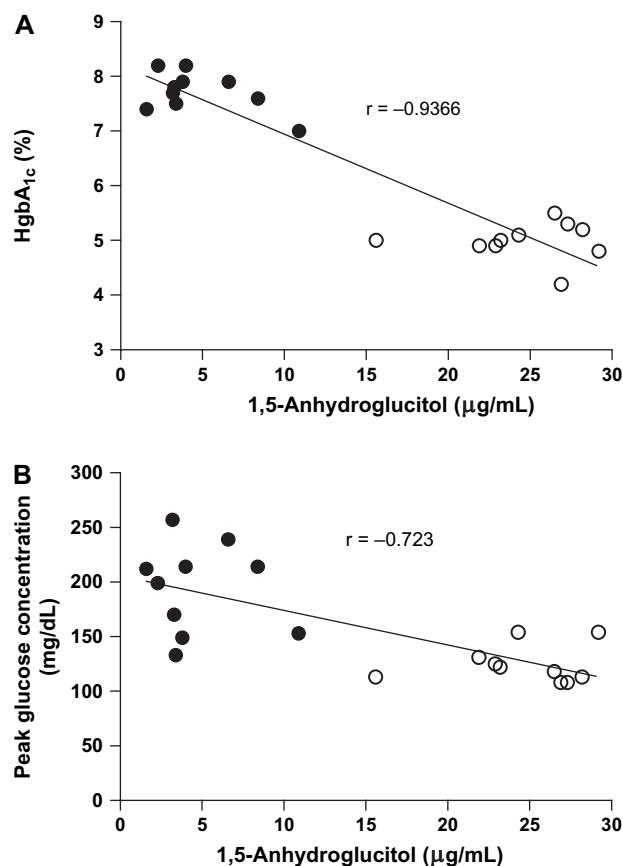


Fig. 2. The correlation between 1,5-anhydroglucitol levels and (A) HgbA_{1c} or (B) peak glucose concentrations in normal children (open circle) and in children with T1DM (filled circle). HgbA_{1c}, glycated hemoglobin A_{1c}; T1DM, type 1 diabetes mellitus.

1988 (18). Our 1,5-AG normal range is in agreement with these studies.

1,5-AG concentrations in patients with diabetes need to be interpreted in context with HbA_{1c}. In our study, children with T1DM had an average HgbA_{1c} of 7.72% and 1,5-AG levels ranged from 1.6 to 10.9 µg/mL. The limitation of our report is that we do not have 1,5-AG levels for children with T1DM in varying degrees of glycemic control. Higher HbA_{1c} is associated with lower 1,5-AG concentrations. However, a caveat to this is that 1,5-AG stores are depleted because of renal losses when HbA_{1c} is chronically high. Table 2 summarizes 1,5-AG levels reported in all studies so far so that a comparison can be made with the available data. 1,5-AG levels were negatively correlated with both HbA_{1c} and peak plasma glucose concentrations after meal. These negative correlations, particularly the one between 1,5-AG and postload glucose, are in agreement with previous studies in the adult with impaired glucose tolerance (10) or with T2DM (19). Dungan et al. in 2006 showed that 1,5-AG concentrations are strongly negatively correlated with overall postmeal maximum glucose concentrations than HgbA_{1c} or FA (3).

Table 1. 1,5-AG concentrations in normal children and adults*

Study	Age-group (yr)	1,5-AG range (µg/mL)			Reference
		Male	Female	Unspecified	
Our data	12–18	15.6–29.2	22.9–28.2	15.6–29.2	
Nowatzke et al. (2004)	≥18	10.2–33.8	5.9–31.8		(16)
Shi et al. (1999)	22–80	29.85 ± 6.46	26.14 ± 8.52	15.11–48.19	(19)
Yamanouchi et al. (1992)	27–68			18.7–35.3	(14)
Yamanouchi et al. (1988)	Mean = 47			23.8 ± 7.2	(18)
Yamanouchi et al. (1987)	18–81			9.6–38.8	(17)

1,5-AG, 1,5-anhydroglucitol.

*Data are expressed as either range or mean ± SD as reported in original studies, except as indicated otherwise.

Plasma 1,5-AG concentrations must be interpreted with caution in patients with renal and hepatic dysfunction or in patients taking herbal medicine. A number of studies show that 1,5-AG levels are influenced by renal threshold for glucose (20) and tubular function (21). For instance, 1,5-AG concentration decreases in adult patients with chronic renal failure (22, 23) and with end-stage renal disease in patients with or without diabetes (24). Continuous ambulatory peritoneal dialysis and hemodialysis lower the plasma 1,5-AG concentrations (24–27). In addition, the plasma 1,5-AG concentrations are also decreased in adult patients with liver cirrhosis (28, 29). There is no published report on plasma 1,5-AG concentrations in children with renal or hepatic dysfunction. The Chinese herbal medicine such as Kampo increases, while acarbose lowers, the plasma

1,5-AG levels in adult patients with T2DM (30, 31). There is no report on the effects of angiotensin converting enzyme (ACE) inhibitors on plasma 1,5-AG levels in children or adults.

A further limitation of our study is that the measurement of 1,5-AG levels, postprandial glucose concentrations, and HgbA1c levels reflect only one point in time. A longitudinal study is planned to study 1,5-AG levels as they correlate to the blood glucose over time in children without and with T1DM. However, these data represent an initial step in this process.

Although the sample size of this study was small, the difference in the 1,5-AG concentration between the groups was statistically significant for the time-point when they are measured. In conclusion, 1,5-AG in children with and without diabetes is in concordance

Table 2. 1,5-AG concentrations in children with T1DM and adults with T1DM and T2DM*

Study	Age-group	HgbA _{1c} (%)	1,5-AG range (µg/mL)			Reference
			T1DM	T2DM	Unspecified	
Our data	12–18	7.72 ± 0.37	1.6–10.9			
Dungan et al. (2006)	18–75	7.29 ± 0.47	3.03–15.6			(3)
		7.30 ± 0.77	3.43–17.5			
Dworacka and Winiarska (2005)	56.1 ± 8.7	7.0 ± 2.3		10.2 ± 6.3		(32)
McGill et al. (2004)	50 ± 11	9.5 ± 1.7			0–10.7	(12)
		8.2 ± 1.2			0.0–15.7	
Shi et al. (1999)	31–85	Not specified		6.41 ± 6.16		(19)
Sone et al. (1996)	62.7 ± 7.4	9.7 ± 1.1		6.8 ± 4.0†		(33)
Kishimoto et al. (1995)	Not specified	6.9 ± 0.6		17.3 ± 6.9		(34)
	Not specified	7.2 ± 0.5		10.7 ± 6.3		
	55.1 ± 7.3	7.1 ± 0.6		6.9 ± 3.3		
	57.6 ± 6.6	7.2 ± 0.5		11.5 ± 5.3		
Yamanouchi et al. (1991)	56.8 ± 13.2	7.9 ± 1.9			5.4 ± 5.1	(11)
		7.2 ± 2.0			8.5 ± 7.3	
Yamanouchi et al. (1988)	18–80				1.9 ± 1.8	(18)
Yamanouchi et al. (1987)	18–81	Not specified			2.1 ± 1.8	(17)
		<8			16.5 ± 2.9	
		8.1–9.0	3.1 ± 1.6		8.0 ± 3.3	
		9.1–10.0	2.0 ± 1.1		4.2 ± 1.7	
		10.1–12.0	0.6 ± 0.9		1.7 ± 0.9	
		>12.1	0.2 ± 0.2		1.0 ± 0.7	

1,5-AG, 1,5-anhydroglucitol; HgbA_{1c}, glycated hemoglobin A_{1c}; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

*Data are expressed as either range or mean ± SD as reported in original studies, except as indicated otherwise.

†44.5 ± 26.1 µmol/L converted to µg/mL, using 20 µg/mL = 130 µM (35).

with reports in adult patients. Further studies are required to determine the 1,5-AG concentrations in children with T1DM in varying glycemic control and in children with renal and hepatic dysfunction. With careful consideration of its limitations, plasma 1,5-AG concentrations may be used in the future to evaluate therapy, especially to target postprandial hyperglycemia in children with T1DM and near normoglycemia.

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