Published in final edited form as:

Diabet Med. 2017 October ; 34(10): 1407–1413. doi:10.1111/dme.13391.

Effects of dietary carbohydrates on 1,5-anhydroglucitol in a population without diabetes: Results from the OmniCarb Trial

Stephen P Juraschek, MD, PhD¹, Edgar R Miller III, MD, PhD¹, Lawrence J Appel, MD, MPH¹, Robert H Christenson, PhD², Frank M. Sacks, MD³, and Elizabeth Selvin, PhD, MPH¹

¹The Johns Hopkins School of Medicine, The Johns Hopkins Bloomberg School of Public Health, and The Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Medical Institutions, Baltimore MD

²University of Maryland School of Medicine

³Harvard T.H. Chan School of Public Health, Harvard Medical School, Brigham & Women's Hospital

Abstract

Background—1,5-anhydroglucitol (1,5-AG) is monosaccharide derived from foods that can be used to monitor hyperglycemic excursions in diabetes. Determinants of 1,5-AG in persons without diabetes are largely uncharacterized and the effects of dietary changes in amount and type of carbohydrates on 1,5-AG are unknown.

Methods—We conducted an ancillary study to a completed, randomized clinical trial in overweight and obese adults without diabetes (N=159). Using a crossover design, participants were fed each of four diets for 5-weeks with 2-week intervening washout periods. The four diets were: high glycemic index (GI 65) with high %carb (58% kcal), low GI (GI 45) with low %carb (40% kcal), low GI with high %carb; and high GI with low %carb. Plasma 1,5-AG was measured at baseline and after each feeding period.

Results—At baseline, participants were mean age 53 years (53% female, 52% non-Hispanic black, 50% obese). Mean fasting glucose and 1,5-AG were 97 mg/dL (5.4 mmol/L) and 18.6 µg/mL (113.3 µmol/L). Compared to baseline, each of the 4 randomized diets reduced 1,5-AG –2.4 to –3.7 µg/mL (–14.6 to –22.5 µmol/L); all *P*-values <0.001). Reducing either glycemic index or proportion of carbohydrates lowered 1,5-AG. These effects were additive, such that reducing both glycemic index and proportion carbohydrate decreased 1,5-AG by –1.31 µg/mL (–1.63, –0.99; *P*<0.001; –8.0; –9.9, –6.0 µmol/L). Furthermore, these effects were confirmed in a subgroup with 12 hour glucose monitoring and no documented hyperglycemia (fasting glucose <160 mg/dL or 8.9 mmol/L).

Address Correspondence to: Stephen P Juraschek, MD, PhD, Johns Hopkins Medical Institutions, 2024 East Monument Street, Suite 1-500, Baltimore, MD 21205, Phone: 410-502-8699, Fax: 410-502-6446, spj@jhmi.edu.

This trial is registered at clinicaltrials.gov, number: NCT00051350.

Conflict of Interest

The authors have no conflicts of interest to report.

Conclusions—Both type and amount of dietary carbohydrates affect 1,5-AG plasma concentrations in adults without diabetes. This finding contradicts the long-standing notion that 1,5-AG remains at constant concentrations in the blood in the absence of hyperglycemic excursions.

Keywords

carbohydrate; diet; glycemic index; 1,5-anhydroglucitol; diabetes; hyperglycemia

The role of diet in the development of diabetes and its impact on biomarkers of glycemia is an ongoing area of debate. Recently the OmniHeart Trial demonstrated that a diet with a higher proportion of carbohydrates decreased insulin sensitivity compared to a diet that had a higher proportion of unsaturated fat (1). Subsequently, The Effect of Amount and Type of Dietary Carbohydrates on Risk for Cardiovascular Heart Disease and Diabetes (OmniCarb) trial demonstrated that in the context of a diet with high carbohydrate content, a low compared to high glycemic index (GI) decreased insulin sensitivity and increased fasting glucose (2).

1,5-anhydroglucitol (1,5-AG) is a monosaccharide found primarily in foods (3). In persons with diabetes, blood concentration of 1,5-AG is an emerging marker of hyperglycemia and glycemic variability. 1,5-AG is inversely associated with blood glucose concentrations due to competitive inhibition by glucose in the proximal tubule (4) and is thought to be useful for intermediate-term monitoring of glycemic variability in people with diabetes (5). In epidemiologic studies, low concentrations have been associated with greater diabetes risk (6,7) and, in the setting of diabetes, with retinopathy, chronic kidney disease (7–9), and cardiovascular disease (10,11). In persons without diabetes, 1,5-AG may reflect carbohydrate digestion (12,13). Little is known about the effects of diet on 1,5-AG, particularly the effects of dietary carbohydrate. The effects of diet on 1,5-AG represent an important source of exogenous variability that remain uncharacterized.

This study was conducted as an ancillary study to the OmniCarb trial, a randomized cross-over dietary intervention (feeding study) of overweight and obese adults without diabetes. In the setting of the OmniCarb trial, our objectives were to quantify and compare the effects of a diet that reduced GI, a diet that reduced proportion of carbohydrates (%carb), or both on 1,5-AG.

METHODS

The rationale, design, and main results from the OmniCarb Trial have been published (2). In brief, the OmniCarb Trial was an investigator-initiated trial sponsored by the National Heart, Lung, and Blood Institute. OmniCarb utilized a cross-over design to compare the effects of altering the quantity or quality of carbohydrates in the context of the DASH diet on cardiovascular disease risk factors (14). The DASH diet is a pattern of healthful eating that emphasizes fruits, vegetables, and low-fat dairy foods with reduced intake of saturated fat, total fat, and cholesterol. Also emphasized in the original DASH diet were whole grains, poultry, fish, and nuts with smaller amounts of red meat, sweets, and sugar-containing beverages (14). The primary outcomes of the original study were: insulin sensitivity

(Matsuda index) (15), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and systolic blood pressure.

We conducted an ancillary study to OmniCarb that used stored plasma specimens to examine the effects of amount and type of carbohydrates on 1,5-AG.

Study Participants

Participants were recruited from areas around Boston, Massachusetts, and Baltimore, Maryland. The trial began in August 2009 and was completed in December 2010. Participants were age 30 years and older with a body mass index (BMI) ≥ 25 kg/m², and had systolic and diastolic blood pressures ranging from 120–159 and 80–99 mmHg, respectively. Persons with a diagnosis of diabetes or cardiovascular disease were excluded from the trial, as were individuals with a fasting glucose >125 mg/dl (6.9 mmol/L) (2). In the present study, we further excluded 4 persons for whom stored blood samples were not available.

Trial Intervention

The trial had a four period, randomized crossover design, in which participants were fed each of four diets for 5-weeks with 2-week intervening washout periods (2). The four diets were: high %carb (58% kcal) with high GI (GI ≥ 65) (CG), low %carb (40% kcal) with low GI (GI ≤ 45) (cg), high %carb with low GI (Cg); and low %carb with high GI (cG). Details of the diets are in Supplemental Table S1. All meals were provided to participants at the study centers. The diets utilized common American foods, but were low in saturated fat, cholesterol, and sodium and rich in fruits, vegetables, fiber, potassium, and other minerals, similar to the DASH diet (14). Calorie targets were determined at baseline based on the body size, sex, and physical activity level of each participant. Adjustments were made to the caloric level throughout the duration of the study to ensure that participants' weight remained within 2% of their baseline weight. Participants were asked to avoid changes in activity levels and alcohol use during the course of the study. Furthermore, each participant listed protocol and non-protocol foods in a diary throughout the study.

Primary outcome: 1,5-anhydroglucitol

Both trial centers utilized the same specimen collection protocols. Fresh whole blood samples were collected at baseline and at the end of each 5-week feeding period (2009–2010) in EDTA tubes. These specimens were immediately spun using a refrigerated centrifuge for 20 minutes at 2400 rpm, and then transferred into cryovials for storage. Plasma specimens were stored in specimen freezers and maintained at -80°C . In 2012, plasma specimens underwent a single thaw cycle for measurement of 1,5-AG (GlycoMark, Winston-Salem, NC), using a Siemens Dimension Vista 1500 chemical analyzer (Siemens Healthcare Diagnostics, Glasgow, DE, Germany) via a two-step enzymatic method (16) that employed spectrophotometry to quantify its concentration. The inter-assay coefficient of variation was 2.4% (mean 14.291 mg/dL or 87.1 $\mu\text{mol/L}$). Prior research suggests that 1,5-AG is robust to a single freeze-thaw cycle (17).

Secondary outcomes: glucose, and insulin

Glucose and insulin were also measured at baseline and at the end of each feeding period as part of the original OmniCarb protocol (2). Serum was collected from fasting participants prior and 2 hours after the administration of a 75g oral glucose bolus. Serum was collected in SST tubes, which were allowed to clot for 30 minutes and then centrifuged in a refrigerated environment for 20 minutes at 2400 rpm. Glucose and insulin were measured shortly after collection throughout the duration of the trial (2009–2010) after a single freeze thaw.

Baseline Characteristics

Baseline characteristics of the participants were determined via questionnaire, laboratory specimens, and physical examination. Body mass index (BMI) was calculated using height and weight measurements. Waist circumference was measured at the level of the umbilicus. Total cholesterol, triglycerides, and high density lipoprotein (HDL) cholesterol were measured in serum. Baseline hypertensive status (yes or no) was determined by an average of 3 baseline blood pressure measurements; hypertension was defined by a systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg.

Statistical Analysis

We compared change in 1,5-AG from baseline (end-of-period minus baseline) after consumption of each of the 5-week diets. We further compared the changes in 1,5-AG between diets, specifically examining the effects of (1) reducing GI in the context of either a low %carb (cg vs. cG) or high %carb (Cg vs. CG) diet, (2) reducing %carb in the context of either a low GI (cg vs. Cg) or high GI (cG vs. CG) diet, or changing both factors simultaneously in the opposite (Cg vs. cG) or same (cg vs. CG) directions. Comparisons were plotted for visual presentation. Comparisons were made with generalized estimating equation (GEE) regression models and a Huber and White robust variance estimator (18), which assumed an exchangeable working correlation matrix. These analyses were repeated for our secondary outcomes, namely, 5-week change in fasting glucose, fasting insulin, 2-hour glucose, and 2-hour insulin. Missing data were rare ($n = 4$) and were evenly distributed between diets and dietary periods.

We also performed a cross-sectional analysis of baseline 1,5-AG and fasting glucose, fasting insulin, 2-hour glucose, and 2-hour insulin. We calculated Pearson's correlation coefficient (r) and performed linear regression with adjustment for age, sex, and race.

Sensitivity analyses were performed to evaluate changes in 1,5-AG in the absence of known glucose excursions. In one sensitivity analysis, we restricted the study population to a group of 37 participants who had glucose measured at the end of each dietary period approximately 14 times over the course of 12 daytime hours. In this subsample, none of the participants had a glucose excursion measured above 160 mg/dL (8.9 mmol/L), the threshold after which serum glucose is thought to influence 1,5-AG concentrations (4). In another sensitivity analysis, we restricted to a population of participants, who maintained a fasting glucose <126 mg/dL (7 mmol/L) and a 2-hour oral glucose tolerance test <200 mg/dL (11.1 mmol/L) in all serum measurements during the course of the trial (this represents a

maximum of five fasting glucose and five 2-hour glucose measurements over a 6 month period) (N = 120).

Finally, we performed a sensitivity analysis in study participants with a diabetes defining glucose measurement at one point during the trial, i.e. at least 1 measured fasting glucose ≥ 126 mg/dL (7 mmol/L) or a 2-hour oral glucose tolerance test ≥ 200 mg/dL (11.1 mmol/L) (N = 39).

All analyses were performed using Stata version 14.0 (Stata Corporation, College Station, TX, USA). Statistical significance was defined as $P < 0.05$. The study protocol was approved by Institutional Review Boards at Johns Hopkins University, Brigham and Women's Hospital, and the Harvard School of Public Health.

RESULTS

Of the 159 participants included in our study, the mean age (standard deviation, SD) was 53 (SD, 11), 53% were women, and 52% were non-Hispanic black (Table 1). The mean BMI was 32 kg/m², and 26% of the study population had hypertension. Baseline measures of fasting glucose ranged from 54 to 146 (mean 97 mg/dl or 3.0 to 8.1 mmol/L; mean 5.4 mmol/L), and baseline 2-hour oral glucose tolerance testing measures ranged from 50 to 297 (mean 136 mg/dL or 2.7 to 16.5 mmol/L; mean 7.5 mmol/L).

Changes from Baseline

1,5-AG concentrations measured at the end of each dietary period were compared to baseline (Table 2). Regardless of the assigned diet during the OmniCarb trial, there were significant reductions in 1,5-AG, ranging from -2.4 to -3.7 $\mu\text{g/mL}$ (-14.6 to -22.5 $\mu\text{mol/L}$) over the course of each feeding period (all P -values for difference from baseline < 0.001). In contrast, there were inconsistent baseline changes in fasting glucose with only the high GI/high %carb and high GI/low %carb diets, showing baseline reductions of -2.5 mg/dL (CG, $P = 0.02$; -0.14 mmol/L) and -2.0 mg/dL (cG, $P = 0.03$; -0.11 mmol/L). There were no significant changes in 2-hour glucose or fasting insulin during each of the feeding periods. However, there was a marginal reduction in 2-hour insulin during the high GI/low %carb diet (-5.1 $\mu\text{U/mL}$ or -36.6 pmol/L; $P = 0.05$).

Between-diet Differences

End-of-period measurements of 1,5-AG were compared between diets to examine the effects of changing GI, %carb, or both factors on plasma concentrations of 1,5-AG (Figure 1). Reducing GI, lowered 1,5-AG by approximately -1 $\mu\text{g/mL}$ (-6 $\mu\text{mol/L}$) in both low and high %carb diets (both P -values < 0.001). In contrast, reducing %carb only significantly lowered 1,5-AG in the context of a high GI diet by -0.5 $\mu\text{g/mL}$ (-3 $\mu\text{mol/L}$) ($P = 0.002$), but not in the context of a low GI diet (-0.2 $\mu\text{g/mL}$ or -1.2 $\mu\text{mol/L}$; $P = 0.18$). Results were additive in that when both factors were reduced simultaneously (cg versus CG), 1,5-AG went down -1.3 $\mu\text{g/mL}$ (-7.9 $\mu\text{mol/L}$) ($P < 0.001$).

Cross-sectional comparison of 1,5-AG with other markers of glucose homeostasis are presented in Table 3. In this population without diabetes, 1,5-AG was not strongly correlated with fasting glucose, 2-hour glucose, fasting insulin, or 2-hour insulin.

In a sensitivity analysis restricted to the 37 participants who had glucose measured over a 12-hour period without a single measurement above 160 mg/dL (8.9 mmol/L), results were virtually identical to our main analysis (Supplemental Table S2). Similarly, results were unchanged when restricted to participants (N = 120) with fasting glucose measures <126 mg/dL (7.0 mmol/L) and 2-hour oral glucose tolerance test measures <200 mg/dL (11.1 mmol/L) at all measurements throughout the trial (Supplemental Table S3). The main findings were also nearly identical in participants who had at least one measured fasting glucose 126 mg/dL (7.0 mmol/L) or a 2-hour oral glucose tolerance test 200 mg/dL (11.1 mmol/L) during the trial (N = 39) (Supplemental Table S4).

DISCUSSION

This study represents one of the only intervention studies to examine the effects of diet on 1,5-AG. We found that adopting a healthful, DASH-style diet significantly reduced 1,5-AG concentrations during the trial. Furthermore, reducing either or both GI and %carb, reduced 1,5-AG in an additive fashion. These effects were further observed in subpopulations with glucose excursions below the threshold necessary to lower 1,5-AG, implying that diet is an independent determinant of 1,5-AG concentrations among persons without diabetes.

1,5-AG is the 1-deoxy form of glucose (4), a monosaccharide derived from foods (4). It is found in high quantities in soybeans, rice, bread, beef, and other plant sources (3). After consumption, 1,5-AG remains metabolically stable and is distributed throughout body organs and tissues (4). 1,5-AG is freely filtered by glomeruli at a rate of 5–10 mg/mL each day and in a healthy person without diabetes it is almost entirely reabsorbed by the proximal renal tubule (4). However, when glucose rises above the renal threshold for glucose, typically >160–180 mg/dL (8.9–10 mmol/L) (4,19), the excess glucose competes with 1,5-AG for reabsorption in the proximal tubule, which in turn increases urine excretion of 1,5-AG and lowers blood concentrations (4,20).

The interpretation of 1,5-AG variation between adults without diabetes is unclear. It is thought that some of the differences between persons may be accounted for by differences in renal reabsorption of 1,5-AG (21). It is also possible that 1,5-AG varies as a result of factors that affect food digestion (for example, microbiota) (12) or nutrient absorption (13). By controlling diets and performing comparisons within person, we are able to isolate the contribution of changes in carbohydrates on 1,5-AG concentrations, independent of mechanisms related to renal or gastrointestinal processes.

Our study excluded persons with a diagnosis of diabetes. As a result, it would be highly unlikely that glucose concentrations would exceed the renal threshold necessary for glucosuria. This was evident in our subsample of 37 participants, who were monitored for 12 hours at the end of each feeding period; none of these participants had a serum glucose concentration exceeding 160 mg/dL (8.9 mmol/L). Thus, the reductions in 1,5-AG compared

to baseline with each of the 4 diets suggests that diet alters 1,5-AG concentrations independently of glycemia in people without diabetes. This is further supported by the observation that fasting glucose concentrations decreased from baseline with the two high GI diets (CG and cG). In a population with diabetes, higher blood glucose with subsequent glycosuria would cause 1,5-AG to lower; however, this was not observed in our population of adults without diabetes.

The dietary effects on 1,5-AG observed in this trial suggest that there may be important dietary determinants of 1,5-AG. It is unclear if these effects are relevant for the interpretation of 1,5-AG in persons with diabetes. Advocates of 1,5-AG have recommended that it be used for short-term (2 week) assessment of glycemic control in response to new treatment regimens (22). Others have suggested it be used to monitor hyperglycemic excursions in persons with diabetes, especially those with a hemoglobin A1c < 8% (5,23–25). 1,5-AG may be useful for diabetes management to the extent that plasma concentrations are maintained at a stable level due to relatively constant, dietary consumption of 1,5-AG, which is in equilibrium with renal excretion (3). However, our study suggests that short-term changes in diet may directly affect 1,5-AG concentrations in the blood by a mean of $-2.4 \mu\text{g/mL}$ ($-14.6 \mu\text{mol/L}$) when changing from a typical American diet (participants' baseline diet) to the high GI/high %carb OmniCarb diet and further by $-1.3 \mu\text{g/mL}$ ($-7.9 \mu\text{mol/L}$) when modestly reducing carbohydrate quantity and quality (cg vs. CG). While these effects may be large enough to be problematic for individuals with a 1,5-AG close to $10 \mu\text{g/mL}$ ($60.9 \mu\text{mol/L}$), a threshold espoused in clinical algorithms, it remains unclear if these dietary effects would be sufficiently large to alter the interpretation of the 1,5-AG in the setting of diabetes, where the overwhelming determinant of 1,5-AG is likely to be elevated glucose.

There are several limitations of this study. All of the four randomized diets were healthy diets, i.e. variants of the DASH diet. While it is likely that the baseline diets of participants were less healthy than the randomized diets, changes from baseline should be interpreted cautiously because this is not a randomized comparison. We could not examine specific diet components and the 1,5-AG content of the diets is unknown. The study also did not include any persons with diabetes. However, study of 1,5-AG in persons without diabetes provided an opportunity to examine the effects of dietary changes on 1,5-AG independent of changes in overt hyperglycemia (6,26). Moreover, while it would seem likely that the observed effects of diet on 1,5-AG would also occur in people with diabetes, it is possible that the magnitude of effect would be dwarfed by the direct effects of hyperglycemia and glycosuria.

Our study also has a number of strengths. The study population was quite diverse in terms of gender and race. We measured 1,5-AG in specimens collected during a double blind, randomized trial with repeat blood collections and multiple measurements of glucose in a population without diabetes or glucose altering medications. This allowed us to examine the within-person effects of diet on 1,5-AG in a population with a low likelihood of glycosuria, removing the primary determinant of 1,5-AG concentrations in individuals with diabetes. Furthermore, the diets were rigorously designed to isolate the effects of GI and %carb on 1,5-AG independently of changes in weight. Finally, in a subsample as part of the original study protocol, glucose concentration was measured at multiple time points over a 12-hour

period providing strong confirmation that the observed effects occurred in absence of glucose elevations and glycosuria.

In conclusion, we found that both the type and amount of dietary carbohydrates affected 1,5-AG concentrations in a population without diabetes, which contradicts the long-standing notion that 1,5-AG remains at constant concentrations in the blood in the absence of hyperglycemic excursions. This could have implications for the interpretation of 1,5-AG. Future studies should examine these and other dietary effects among persons with and without diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding for this study was provided through grants HL084568 and HL084568 from the National Institutes of Health.

The following companies donated food: The Almond Board, International Tree Nut Council, Olivio Premium Products Inc, and The Peanut Institute.

SPJ is supported by a NIH/NIDDK T32DK007732-20 Renal Disease Epidemiology Training Grant.

This trial is registered at clinicaltrials.gov, number: NCT00608049.

ERM was supported by a NIH R01 ancillary grant.

The GlycoMark corporation provided materials for the 1,5-anhydroglucitol assay.

This trial is registered at clinicaltrials.gov, number: NCT00608049.

Abbreviations used

OmniCarb	The Effect of Amount and Type of Dietary Carbohydrates on Risk for Cardiovascular Heart Disease and Diabetes Study
CG	the high carbohydrate, high glycemic index diet
cG	the low carbohydrate, high glycemic index diet
Cg	the high carbohydrate, low glycemic index diet
cg	the low carbohydrate, low glycemic index diet
1,5-AG	1,5-anhydroglucitol
BMI	body mass index
LDL	low density lipoprotein
HDL	high density lipoprotein
GEE	generalized estimating equation

CI confidence interval

References

1. Gadgil MD, Appel LJ, Yeung E, Anderson CAM, Sacks FM, Miller ER 3rd. The Effects of Carbohydrate, Unsaturated Fat, and Protein Intake on Measures of Insulin Sensitivity: Results from the OmniHeart Trial. *Diabetes Care*. 2012 Dec 5.
2. Sacks FM, Carey VJ, Anderson CAM, Miller ER, Copeland T, Charleston J, et al. Effects of high vs low glycemic index of dietary carbohydrate on cardiovascular disease risk factors and insulin sensitivity: the OmniCarb randomized clinical trial. *JAMA*. 2014 Dec 17; 312(23):2531–41. [PubMed: 25514303]
3. Yamanouchi T, Tachibana Y, Akanuma H, Minoda S, Shinohara T, Moromizato H, et al. Origin and disposal of 1,5-anhydroglucitol, a major polyol in the human body. *Am J Physiol*. 1992 Aug; 263(2 Pt 1):E268–273. [PubMed: 1514606]
4. Buse JB, Freeman JLR, Edelman SV, Jovanovic L, McGill JB. Serum 1,5-anhydroglucitol (GlycoMark): a short-term glycemic marker. *Diabetes Technol Ther*. 2003; 5(3):355–63. [PubMed: 12828817]
5. Dungan KM. 1,5-anhydroglucitol (GlycoMark) as a marker of short-term glycemic control and glycemic excursions. *Expert Rev Mol Diagn*. 2008 Jan; 8(1):9–19. [PubMed: 18088226]
6. Juraschek SP, Steffes MW, Miller ER 3rd, Selvin E. Alternative markers of hyperglycemia and risk of diabetes. *Diabetes Care*. 2012 Nov; 35(11):2265–70. [PubMed: 22875225]
7. Selvin E, Rawlings AM, Grams M, Klein R, Steffes M, Coresh J. Association of 1,5-anhydroglucitol with diabetes and microvascular conditions. *Clin Chem*. 2014 Nov; 60(11):1409–18. [PubMed: 25200356]
8. Selvin E, Francis LMA, Ballantyne CM, Hoogeveen RC, Coresh J, Brancati FL, et al. Nontraditional markers of glycemia: associations with microvascular conditions. *Diabetes Care*. 2011 Apr; 34(4):960–7. [PubMed: 21335368]
9. Parrinello CM, Sharrett AR, Maruthur NM, Bergenstal RM, Grams ME, Coresh J, et al. Racial Differences in and Prognostic Value of Biomarkers of Hyperglycemia. *Diabetes Care*. 2016 Apr; 39(4):589–95. [PubMed: 26681712]
10. Liang M, McEvoy JW, Chen Y, Sharrett AR, Selvin E. Association of a Biomarker of Glucose Peaks, 1,5-Anhydroglucitol, With Subclinical Cardiovascular Disease. *Diabetes Care*. 2016 Oct; 39(10):1752–9. [PubMed: 27481841]
11. Selvin E, Rawlings A, Lutsey P, Maruthur N, Pankow JS, Steffes M, et al. Association of 1,5-Anhydroglucitol With Cardiovascular Disease and Mortality. *Diabetes*. 2016 Jan; 65(1):201–8. [PubMed: 26395741]
12. Yamaguchi Y, Adachi K, Sugiyama T, Shimozaoto A, Ebi M, Ogasawara N, et al. Association of Intestinal Microbiota with Metabolic Markers and Dietary Habits in Patients with Type 2 Diabetes. *Digestion*. 2016; 94(2):66–72. [PubMed: 27504897]
13. Pitkänen E, Pitkänen O. The elimination of 1,5-anhydroglucitol administered to rats. *Experientia*. 1984 May 15; 40(5):463–5. [PubMed: 6723908]
14. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med*. 1997 Apr 17; 336(16):1117–24. [PubMed: 9099655]
15. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care*. 1999 Sep; 22(9):1462–70. [PubMed: 10480510]
16. Fukumura Y, Tajima S, Oshitani S, Ushijima Y, Kobayashi I, Hara F, et al. Fully enzymatic method for determining 1,5-anhydro-D-glucitol in serum. *Clin Chem*. 1994 Nov; 40(11 Pt 1):2013–6. [PubMed: 7955370]
17. Selvin E, Rynders GP, Steffes MW. Comparison of two assays for serum 1,5-anhydroglucitol. *Clin Chim Acta*. 2011 Apr 11; 412(9–10):793–5. [PubMed: 21238440]
18. White H. A heteroskedasticity-consistent covariance matrix estimator and a direct test for heteroskedasticity. *Econometrica*. 1980; 48(4):817–38.

19. Yamanouchi T, Minoda S, Yabuuchi M, Akanuma Y, Akanuma H, Miyashita H, et al. Plasma 1,5-anhydro-D-glucitol as new clinical marker of glycemic control in NIDDM patients. *Diabetes*. 1989 Jun; 38(6):723–9. [PubMed: 2656341]
20. Akanuma Y, Morita M, Fukuzawa N, Yamanouchi T, Akanuma H. Urinary excretion of 1,5-anhydro-D-glucitol accompanying glucose excretion in diabetic patients. *Diabetologia*. 1988 Nov; 31(11):831–5. [PubMed: 3234638]
21. Hasslacher C, Kulozik F. Effect of renal function on serum concentration of 1,5-anhydroglucitol in type 2 diabetic patients in chronic kidney disease stages I–III: A comparative study with HbA1c and glycated albumin. *J Diabetes*. 2016 Sep; 8(5):712–9. [PubMed: 26615054]
22. The Johns Hopkins University. The Johns Hopkins POC-IT DIABETES Guide. 2010.
23. Dungan KM, Buse JB, Largay J, Kelly MM, Button EA, Kato S, et al. 1,5-anhydroglucitol and postprandial hyperglycemia as measured by continuous glucose monitoring system in moderately controlled patients with diabetes. *Diabetes Care*. 2006 Jun; 29(6):1214–9. [PubMed: 16731998]
24. Kim WJ, Park CY, Park SE, Rhee EJ, Lee WY, Oh KW, et al. Serum 1,5-anhydroglucitol is associated with diabetic retinopathy in Type 2 diabetes. *Diabet Med*. 2012 Sep; 29(9):1184–90. [PubMed: 22332964]
25. Kim WJ, Park C-Y. 1,5-Anhydroglucitol in diabetes mellitus. *Endocrine*. 2013 Feb; 43(1):33–40. [PubMed: 22847316]
26. Juraschek SP, Steffes MW, Selvin E. Associations of alternative markers of glycemia with hemoglobin a1c and fasting glucose. *Clin Chem*. 2012 Dec; 58(12):1648–55. [PubMed: 23019309]

Novelty Statements

- 1,5-anhydroglucitol (1,5AG) is an emerging marker of hyperglycemia that is reduced in the blood in the setting of elevated glucose levels.
- However, 1,5AG is originally derived from diet and it is unknown how diet impacts this marker, which could have implications for its interpretation.
- In a tightly controlled feeding study of adults without diabetes, we show that both type and proportion of carbohydrates influence 1,5AG levels independent of hyperglycemia.
- This finding contradicts the long-standing notion that 1,5-AG remains at constant concentrations in the blood in the absence of hyperglycemic excursions.

Difference in 1,5-Anhydroglucitol Between Diets

Figure 1.

Change in 1,5-anhydroglucitol (μg/mL, 95% confidence intervals) between diets (N = 159). Comparisons are organized by dietary factor: glycemic index, proportion carbohydrate, or both factors. CG represents the high carbohydrate/high glycemic index diet. Cg represents the high carbohydrate/low glycemic index diet, cG represents the low carbohydrate/high glycemic index diet, and cg represents the low carbohydrate/low glycemic index diet. Convert 1,5-AG from μg/mL to μmol/L by multiplying by 6.0918.

Table 1

Baseline characteristics of trial participants with stored specimens (N = 159), mean (SD) or No. (%)

Age, y	52.5 (11.2)
Women	85 (53)
Race **	
Non-Hispanic White	65 (41)
Non-Hispanic Black	82 (52)
Hispanic	9 (6)
Asian	3 (2)
Body mass index, kg/m ²	32.3 (5.6)
Body mass index	
25–29.9	69 (43)
30	90 (57)
Waist circumference, cm	104.3 (13.5)
Homeostasis model assessment (HOMA), unit	1.9 (1.6)
Triglycerides, mg/dL	104.8 (67.7)
HDL cholesterol, mg/dL	58.3 (15.9)
LDL cholesterol, mg/dL	153.2 (42.4)
Systolic blood pressure, mm Hg	132.1 (9.1)
Diastolic blood pressure, mm Hg	80.0 (7.4)
Baseline hypertension status *	
No hypertension	117 (74)
Hypertension	42 (26)

* Defined as baseline SBP ≥140 or DBP ≥90 mmHg

** Does not sum to 100% due to rounding

Convert triglycerides from mg/dL to mmol/L by multiplying by 0.0113. Convert HDL and LDL cholesterol from mg/dL to mmol/L by multiplying by 0.0259.

Table 2

Change in 1,5-anhydroglucitol from baseline

		Mean (95% Confidence Interval) Change from Baseline by Diet											
		High Carbohydrate/High Glycemic Index (CG)			High Carbohydrate/Low Glycemic Index (CG)			Low Carbohydrate/High Glycemic Index (cG)			Low Carbohydrate/Low Glycemic Index (cg)		
	No.	Baseline Mean (SD)	Difference, 95% CI	P	Difference, 95% CI	P	Difference, 95% CI	P	Difference, 95% CI	P	Difference, 95% CI	P	
1,5-AG (µg/mL)	159	18.6 (5.8)	-2.38 (-2.86, -1.90)	<0.001	-3.47 (-3.97, -2.98)	<0.001	-2.91 (-3.41, -2.41)	<0.001	-3.69 (-4.20, -3.18)	<0.001			
Glucose (mg/dL)	159	97.3 (13.7)	-2.50 (-4.65, -0.35)	0.02	-0.85 (-2.80, 1.10)	0.39	-2.04 (-3.88, -0.20)	0.03	0.15 (-1.60, 1.90)	0.87			
2-hour glucose (mg/dl)	159	135.6 (43.0)	3.89 (-1.29, 9.06)	0.14	0.40 (-4.68, 5.49)	0.88	3.94 (-1.60, 9.49)	0.16	3.21 (-2.18, 8.59)	0.24			
Insulin (µU/mL)	159	7.7 (5.8)	-0.76 (-1.56, 0.04)	0.06	0.19 (-0.88, 1.26)	0.73	-0.61 (-1.45, 0.24)	0.16	-0.24 (-1.15, 0.66)	0.60			
2-hour insulin (µU/mL)	159	49.0 (43.5)	-0.04 (-8.58, 8.49)	0.99	-1.46 (-7.59, 4.67)	0.64	-5.07 (-10.08, -0.06)	0.05	-0.47 (-5.62, 4.69)	0.86			

Note: Convert 1,5-AG from µg/mL to µmol/L by multiplying by 6.0918. Convert glucose from mg/dL to mmol/L by dividing by 18. Convert insulin µU/mL to pmol/L by multiplying by 7.175.

Table 3

Pearson correlation coefficients (r) and linear regression coefficients (β) and between 1,5-anhydroglucitol, glucose, and insulin measured at baseline

	1,5-anhydroglucitol, $\mu\text{g/mL}$ (N=159)			
	r	β	Standard Error	P^*
Serum fasting glucose, mg/dL	−0.12	−0.06	0.03	0.09
Serum 2-hr glucose, mg/dl	−0.11	−0.01	0.01	0.21
Serum fasting insulin, $\mu\text{U/mL}$	0.00	−0.03	0.08	0.71
Serum 2-hr insulin, $\mu\text{U/mL}$	−0.08	−0.01	0.01	0.35

* P -value for ordinary least squares coefficient (β) adjusted for age, sex, and race/ethnicity

Note: Convert 1,5-AG from $\mu\text{g/mL}$ to $\mu\text{mol/L}$ by multiplying by 6.0918. Convert glucose from mg/dL to mmol/L by dividing by 18. Convert insulin $\mu\text{U/mL}$ to pmol/L by multiplying by 7.175.