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Response of 1,5-anhydroglucitol to intensive glucose- and blood-pressure lowering interventions, and its associations with clinical outcomes in the ADVANCE trial

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ABSTRACT

Background: Low 1,5-anhydroglucitol (1,5-AG) is a marker of glycosuric hyperglycemia. We evaluated 1,5-AG with clinical outcomes and assessed the effects of glucose- and blood pressure-lowering interventions on change in 1,5-AG in type 2 diabetes.

Methods: We measured 1,5-AG in 6,826 stored samples at baseline and a random subsample of 684 participants at the 1-year follow-up visit in the ADVANCE trial. We examined baseline 1,5-AG (<6, 6-10, ≥ 10 ug/mL) with microvascular and macrovascular events and mortality using Cox regression models during 5 years of follow-up. Using an intention-to-treat approach, we examined 1-year change in 1,5-AG (mean and percent) in response to the glucose- and blood pressure-lowering interventions in the subsample.

Results: Low 1,5-AG (<6 ug/mL vs ≥ 10 ug/mL) was associated with microvascular events (HR 1.28, 95%CI 1.03-1.60) after adjustment for risk factors and baseline HbA1c. However, the associations for macrovascular events and mortality were not independent of HbA1c. The glucose-lowering intervention was associated with a significant 1-year increase in 1,5-AG (vs standard control) of 1.01 ug/mL (SE, 0.38), corresponding to an 8.26% (SE, 0.10) increase from baseline. We also observed an increase in 1,5-AG of similar magnitude in response to the blood pressure intervention independent of the glucose-lowering effect.

Conclusions: Our results suggest that 1,5-AG is a marker of risk in adults with type 2 diabetes, but only for microvascular events independently of HbA1c. We found that 1,5-AG was improved (increased) in response to an intensive glucose-lowering intervention, although the independent

effect of the blood pressure-lowering intervention on 1,5-AG suggests potential non-glycemic influences.

1,5-anhydroglucitol (1,5-AG) is an emerging biomarker that is of growing interest for monitoring hyperglycemia in individuals with diabetes. 1,5-AG is a monosaccharide (deoxy-1 form of glucose) derived primarily from food and that is typically maintained at stable concentrations in the blood (1). However, when blood glucose concentrations exceed the renal threshold (i.e., 140-160 mg/dL), 1,5-AG competes with glucose for reabsorption in the renal proximal tubule and is excreted in the urine. Thus, periods of hyperglycemic excursions will lower blood concentrations of 1,5-AG. Low 1,5-AG is thought to be a useful biomarker to monitor glycosuric hyperglycemia. 1,5-AG has been linked to complications of diabetes in prior observational studies (2-7), but few reports have examined how 1,5-AG may respond to an intensive glucose-lowering intervention. Prior trials have been small and of short duration (a few weeks or less) (8-12).

We conducted measurements of 1,5-AG in stored blood samples in an ancillary study to the completed Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Research Controlled Evaluation (ADVANCE) factorial trial to examine the associations of baseline 1,5-AG with long-term microvascular and macrovascular outcomes and mortality and also the response of 1,5-AG to intensive glucose-lowering and blood pressure reduction interventions.

METHODS

Study Population

ADVANCE is a completed two-by-two factorial randomized controlled trial that was designed to examine the effects of a fixed combination of blood pressure-lowering drugs (the angiotensin converting enzyme (ACE) inhibitor perindopril (4 mg) and the thiazide-diuretic indapamide (1.25 mg)), vs placebo, and an intensive glucose-lowering intervention (gliclazide modified release-based intervention) with a target HbA1c of <6.5% vs standard control arm (target HbA1c based on local guidelines) on microvascular and macrovascular events (13, 14). The trial was conducted in 215 collaborating centers in 20 different countries and enrolled 11,140 participants with type 2 diabetes who were followed for major microvascular and macrovascular endpoints. As part of the original protocol, blood was collected for long-term storage at baseline (2001-2003) in all participants and in a 10% random sample of participants at the 1-year follow-up visit. Due to national policies on the transfer of biological material, stored samples were not available from the clinical centers in India or China (~20% of ADVANCE participants). We retrieved stored blood samples from 7,283 participants at baseline; valid measurements of 1,5-AG were obtained from 7,278. For the present study, we further excluded those participants who were missing covariates of interest at baseline for a final study sample of 6,826. There were 684 participants who also had stored blood available and valid measurements of 1,5-AG at the 1-year visit.

Approval for the ADVANCE trial was obtained from the ethics committee of each clinical center and all participants provided written informed consent. The ADVANCE ancillary

biomarker study presented here was also approved by the institutional review boards of the Johns Hopkins Bloomberg School of Public Health and the University of Minnesota.

Laboratory Measurements

We measured 1,5-AG in EDTA lithium-heparin plasma samples using an enzymatic colorimetric method (GlycoMark, Inc) implemented on a Roche Cobas 6000 analyzer (Roche Diagnostics, Indianapolis, IN) at the Advanced Research and Diagnostic Laboratory at the University of Minnesota Medical Center. The inter-assay CVs were 0.9% at a mean concentration of 18.0 ug/mL and 9.7% at a mean concentration of 3.8 ug/mL. All other laboratory measurements were conducted by local laboratories as part of the original ADVANCE trial protocol (13, 14).

Outcomes

We examined here the primary outcome of the original trial, a composite of macrovascular and microvascular events, considered jointly and separately. Macrovascular events were defined as death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

Microvascular events included new or worsening nephropathy (development of macroalbuminuria, doubling of serum creatinine level to at least 200 umol/L, the need for renal replacement therapy, death due to renal disease), or retinopathy (13, 14). We also examined all-cause mortality. All trial outcomes were adjudicated by an endpoints committee.

Statistical Analyses

We undertook two main analyses. First, we examined the observational association of baseline 1,5-AG with all four clinical outcomes in the overall population included in the present study.

Second, we examined the effects of the glucose- and blood-pressure lowering interventions (intention-to-treat analysis) on change in 1,5-AG from baseline to the 1-year follow-up visit in the 10% random subsample.

For the observational analyses, we summarized the characteristics of the ADVANCE study participants at baseline overall and according to categories of 1,5-AG (<6, 6-10, ≥ 10 ug/mL). We used Cox regression models to examine the association of categories of 1,5-AG with all four clinical outcomes, with adjustment for potential confounding variables.

Model 1 was adjusted for age, sex, region, glucose treatment arm, and blood pressure treatment arm. Model 2 was adjusted for all variables in Model 1 plus history of cardiovascular disease, history of microvascular disease, estimated glomerular filtration rate (eGFR), and albumin-to-creatinine ratio. Model 3 was adjusted for all variables in Model 2 plus HbA1c to evaluate whether any association of 1,5-AG was independent of baseline glycemic control. We also modeled 1,5-AG as a restricted cubic spline to more flexibly evaluate the continuous association with each of the four outcomes (15). For the spline, we included four knots, placed at the 5th, 35th, 65th and 95th percentiles (2.8, 8.3, 14.5, and 26.3 ug/mL, respectively). Finally, we examined the associations of 1,5-AG with the outcomes stratified by category of HbA1c at baseline (<7% vs $\geq 7\%$).

For the intention-to-treat analysis of the glucose- and blood-pressure lowering interventions on 1-year change in 1,5-AG, we evaluated the within-group differences in mean 1,5-AG at 1-year by treatment arm and the between-group difference (intensive vs standard

control or active drug vs placebo). We also compared the percentage change in 1,5-AG by treatment arm overall and by categories (>25% decrease, 10-25% decrease, stable ($\pm 10\%$), 10-25% increase, >25% increase). We also examined the combined effect of the glucose-e and blood pressure-lowering interventions on 1-year change in 1,5-AG (2-by-2 factorial design).

RESULTS

The characteristics of the two study populations included here were similar to the original baseline study population of ADVANCE (**eTable 1**). In our overall population of 6,826 adults with type 2 diabetes from the ADVANCE trial, those participants with lower levels of 1,5-AG were more likely to be male, have a longer duration of diabetes, have a history of microvascular disease at baseline, and have albuminuria (**Table 1**). Mean fasting glucose and HbA1c levels were higher among individuals in the lower categories of 1,5-AG. The overall Spearman's rank correlations coefficients for 1,5-AG with fasting glucose and HbA1c were -0.49 and -0.55, respectively (**eFigure 1**). These correlations were lower at higher concentrations of 1,5-AG (i.e., the associations were not strictly linear).

During a median of approximately 5 years of follow-up, there were 1,229 incident combined microvascular and macrovascular events, 691 macrovascular events, 607 microvascular events, and 686 deaths among the 6,826 participants at baseline. There was a robust inverse association of categories of 1,5-AG with the composite outcome (combination of incident microvascular or macrovascular events), microvascular events, and mortality in Models 1 and 2 (**Table 2**). Associations with incident macrovascular events, alone, were weaker. After

adjustment for HbA1c, the inverse associations with combined microvascular and macrovascular events, macrovascular events, and mortality were strongly attenuated, although the association between the lowest and highest categories of 1,5-AG (<6 ug/mL vs ≥ 10 ug/mL) with microvascular events remained significant (HR 1.28, 95%CI 1.03, 1.60, $p < 0.05$). The inverse association of 1,5-AG with microvascular events was generally linear at concentrations of 10 ug/mL or lower (**Figure 1**). At concentrations greater than 15 ug/mL, there was no evidence for an association of 1,5-AG with any of the outcomes. When stratified by baseline categories of HbA1c, the strongest associations were for those individuals with elevated HbA1c ($\geq 7\%$) and low 1,5-AG (<10 ug/mL) (**eTable 2**).

In the intention-to-treat analysis of our $\sim 10\%$ subsample of participants with 1,5-AG measurements at both baseline and 1-year of follow-up, we observed a significant increase in mean 1,5-AG in the intensively treated group compared to the standard arm ($p = 0.008$) (**Figure 2, Panel A; eTable 3**). The percentage change in the intensive arm was $+7.77\%$ compared to -0.48% in the standard arm (**eTable 3**). Indeed, 35.3% of participants had a greater than 25% increase in 1,5-AG in the intensive arm at 1-year compared to only 25.0% in the standard arm.

In our analysis of the effect of the blood pressure-lowering intervention on 1,5-AG at 1-year, we found that the blood pressure intervention also increased 1,5-AG ($p = 0.0012$) (**Figure 2, Panel B**). In the analysis of the 2×2 factorial intervention, we observed the greatest effect on 1,5-AG in those participants who received both the blood pressure and glucose-lowering interventions (**eTable 4; eFigure 2, Panel A**). Those individuals who were in the intensive

glucose treatment arm and also in the active blood pressure drug treatment arm had a significant 12.68% increase in 1,5-AG at 1-year (compared to a significant decrease in the standard glucose arm plus blood pressure placebo group). In the combined treatment group, 43.4% of participants had a >25% increase in 1,5-AG. This is in contrast to HbA1c which was reduced by the glucose-lowering intervention but not independently by the blood pressure-lowering intervention (**eTable 4; eFigure 2, Panel B**).

DISCUSSION

In this ancillary study to the ADVANCE trial, we observed that baseline 1,5-AG concentrations were inversely associated with microvascular outcomes. 1,5-AG was also inversely associated with macrovascular outcomes and mortality, but these associations were not robust to adjustment for baseline HbA1c. We found that after 1-year of follow-up, 1,5-AG concentrations improved (increased) in response to the intensive glucose-lowering intervention. Because 1,5-AG is lowered in the setting of hyperglycemia, this demonstrates a significant improvement in 1,5-AG concentrations (i.e., a reduction in glycosuric hyperglycemia) in the intensively treated arm. We also observed that the blood pressure treatment with an ACE inhibitor (perindopril) and thiazide diuretic (indapamide) raised 1,5-AG. The greatest effect on 1-year change in 1,5-AG was observed in those individuals who received both the glucose- and blood-pressure lowering interventions.

Our results for the observational analysis of baseline 1,5-AG with microvascular and macrovascular events in the ADVANCE Trial is consistent with prior studies in populations of persons with type 2 diabetes (2-7, 16). In analyses of the Atherosclerosis Risk in Communities (ARIC) Study, we previously reported that 1,5-AG was inversely associated with prevalent retinopathy and incident chronic kidney disease (6), incident end stage renal disease (2), and incident cardiovascular disease and mortality (5). In adults with type 2 diabetes in the ARIC Study, the risk associations were highly similar to those observed here in the ADVANCE trial study population. The threshold effect around 10 to 15 ug/mL—where there were risk associations below but not above this level—is also consistent with prior reports (5, 6). Our results in ADVANCE suggest that high 1,5-AG concentrations (>15 ug/mL) do not reflect hyperglycemia-related processes and are not associated with clinical outcomes. Indeed, there is little to no correlation of 1,5-AG with measures of hyperglycemia when 1,5-AG concentrations exceed 10 to 15 ug/mL (6).

Few prior studies have examined the response of 1,5-AG to an intensive glucose lowering intervention. We found that a glimepiride-based strategy to improve glucose control had a significant effect on 1,5-AG concentrations. We also found that the blood pressure intervention had a similar effect on 1,5-AG. That is, we observed an independent effect of the blood pressure-lowering intervention on 1,5-AG beyond the impact of the glucose-lowering intervention. Whereas, the blood pressure intervention did not have a significant effect on 1-year change in HbA1c. ACE inhibitors such as perindopril lower intraglomerular pressure and are known to

have renal-protective effects (17, 18). Because 1,5-AG is reabsorbed into the blood in the renal proximal tubule, it is plausible that improvement in the function of the proximal tubule could result in increases in serum 1,5-AG independent of changes in glucose control. Nonetheless, we are unable to discern if the improvement in 1,5-AG was due to an independent effect of the ACE inhibitor or improved blood pressure control more generally.

Limitations of this study include that we only had measurements of 1,5-AG in participants at baseline and a 10% subsample at the 1-year examination. We also were not able to obtain blood samples from the Indian and Chinese centers and thus our study sample in the observational analyses was smaller than the original ADVANCE study (missing 34.7% of participants). Nonetheless, characteristics of the study populations included here were not substantially different than the original cohort. The lack of additional follow-up information on 1,5-AG is a weakness in that we were unable to rigorously examine long-term changes in 1,5-AG or their associations with outcomes. Because we observed a significant improvement in 1,5-AG levels in response to the glucose lowering intervention at 1-year, it is possible that the observational results may have been attenuated as a result of the success of the glucose lowering intervention in improving microvascular and macrovascular risk in the main trial.

In conclusion, we found that an intensive glucose-lowering intervention resulted in a significant 1-year change in 1,5-AG—a marker of glycosuric hyperglycemia—in a diverse study population of adults with type 2 diabetes. We also observed a novel effect of a blood pressure lowering intervention on change in 1,5-AG which was similar in magnitude to but independent

of improvements in glucose control. Our study confirmed the association of low 1,5-AG with long-term outcomes, particularly incident microvascular disease. Nonetheless, the clinical utility of targeting or monitoring 1,5-AG in diabetes care is not yet established. Ultimately, our findings support the prognostic value of 1,5-AG in type 2 diabetes but also raise questions about glucose-independent effects on serum concentrations of 1,5-AG.

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Author contributions: E.S. and M.W contributed to the concept and rationale for the study and interpretation of the results. E.S. drafted the manuscript. D.W. conducted the statistical analysis with supervision from E.S. All authors contribution to the discussion and reviewed and edited the manuscript. E.S. and M.W. are the guarantors of this work and as such, had access to all the data in the study and take full responsibility for the accuracy of the data analysis.

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Table 1. Baseline characteristics of participants according to categories of 1,5-anhydroglucitol (1,5-AG), ADVANCE Biomarker Study Population (n = 6826)

	Overall (N = 6826)	1,5-AG < 6 µg/mL (N = 1515)	1,5-AG 6 to <10 µg/mL (N = 1468)	1,5-AG ≥ 10 µg/mL (N = 3843)
Mean age (SD), y	66.4 (6.5)	65.4 (6.4)	66.7 (6.5)	66.6 (6.6)
Female, %	39.7	35.1	37.6	42.4
Blood pressure treatment, %				
Placebo	50.2	48.9	48.9	51.2
Active drug*	49.8	51.1	51.1	48.8
Glucose treatment, %				
Standard control	50.1	51.5	48.8	50.0
Intensive control	49.9	48.5	51.2	50.0
Region, %				
Australia and New Zealand	19.7	18.5	20.6	19.8
Asia	9.1	10.1	8.2	9.0
Europe	66.2	64.0	64.9	67.6
North America	5.0	7.4	6.3	3.5
Mean body mass index (SD), kg/m ²	29.7 (5.3)	29.6 (5.2)	29.5 (5.3)	29.8 (5.3)
Mean duration of diabetes (SD), y	7.9 (6.5)	9.3 (6.6)	8.6 (6.7)	7.1 (6.2)
History of macrovascular disease, %	32.9	31.4	31.9	33.9
History of microvascular disease, %	9.8	11.9	11.0	8.5
Smoking status, %				

Never smoker	49.4	50.0	46.7	50.2
Former smoker	37.2	36.4	40.4	36.3
Current smoker	13.4	13.6	12.9	13.5
Mean total cholesterol (SD), mg/dL	197.8 (44.7)	197.9 (45.8)	196.1 (42.0)	198.3 (45.3)
Mean HDL cholesterol (SD), mg/dL	47.2 (12.7)	45.3 (11.7)	47.0 (12.7)	48.0 (13.0)
Mean triglycerides (SD), mg/dL	171.4 (106.2)	189.6 (120.5)	173.3 (108.8)	163.6 (98.1)
Mean systolic blood pressure (SD), mm Hg	146.8 (21.2)	146.8 (21.4)	146.9 (21.3)	146.7 (21.1)
Mean diastolic blood pressure (SD), mm Hg	81.4 (10.8)	82.0 (10.8)	81.2 (10.9)	81.2 (10.7)
Mean fasting Glucose (SD), mg/dL	151.1 (48.0)	190.8 (57.4)	155.4 (45.0)	133.8 (33.0)
Mean HbA1c (SD), %	7.4 (1.4)	8.7 (1.6)	7.6 (1.2)	6.8 (1.0)
eGFR < 60 mL/min/1.73m ² , %	19.8	15.7	19.1	21.7
Albumin: creatinine ratio > 30 µg/mg, %	27.6	33.1	28.8	25.0

Abbreviations: ADVANCE, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; HDL, high-density lipoprotein; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate.

* Perindopril-indapamide

Table 2. Association of baseline categories of 1,5-anhydroglucitol (1,5-AG) with macrovascular and microvascular events and mortality, ADVANCE Biomarker Study Population (n = 6826)

	N event / N total	Model 1* HR (95% CI)	Model 2† HR (95% CI)	Model 3‡ HR (95% CI)
Combined macrovascular and microvascular events				
1,5 AG Levels				
≥ 10 µg/mL	615/3843	1 (ref)	1 (ref)	1 (ref)
6 to < 10 µg/mL	281/1468	1.22 (1.06, 1.40)	1.22 (1.06, 1.41)	1.06 (0.91, 1.22)
< 6 µg/mL	333/1515	1.44 (1.26, 1.65)	1.43 (1.25, 1.64)	1.04 (0.89, 1.22)
Macrovascular events				
1,5 AG Levels				
≥ 10 µg/mL	368/3843	1 (ref)	1 (ref)	1 (ref)
6 to < 10 µg/mL	164/1468	1.17 (0.97, 1.41)	1.18 (0.98, 1.42)	1.05 (0.87, 1.27)
< 6 µg/mL	159/1515	1.16 (0.97, 1.40)	1.17 (0.97, 1.41)	0.88 (0.71, 1.10)
Microvascular event				
1,5 AG Levels				
≥ 10 µg/mL	278/3843	1 (ref)	1 (ref)	1 (ref)
6 to < 10 µg/mL	132/1468	1.28 (1.04, 1.58)	1.27 (1.03, 1.56)	1.09 (0.88, 1.35)
< 6 µg/mL	197/1515	1.80 (1.50, 2.17)	1.76 (1.47, 2.12)	1.28 (1.03, 1.60)
All-cause mortality				
1,5 AG Levels				
≥ 10 µg/mL	359/3843	1 (ref)	1 (ref)	1 (ref)
6 to < 10 µg/mL	168/1468	1.25 (1.04, 1.50)	1.25 (1.04, 1.51)	1.14 (0.94, 1.38)
< 6 µg/mL	159/1515	1.22 (1.02, 1.48)	1.22 (1.01, 1.47)	0.97 (0.78, 1.21)

ADVANCE, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation

* Model 1: adjusted for age, sex, region, glucose treatment arm, and blood pressure treatment arm

† Model 2: adjusted for all variables in Model 1 plus history of macrovascular disease, history of microvascular disease, estimated glomerular filtration rate, and albumin-to-creatinine ratio

‡ Model 3: adjusted for all variables in Model 2 plus hemoglobin A1c

Figure 1. Adjusted associations for baseline 1,5-anhydroglucitol with macrovascular events, microvascular events and mortality in ADVANCE biomarker subsample.

Hazard ratios are from Cox proportional hazards models adjusted for age, sex, region, glucose treatment arm, blood pressure treatment arm, history of macrovascular disease, history of microvascular disease, estimated glomerular filtration rate, and albumin-to-creatinine ratio. Baseline 1,5-AG was modeled using a restricted cubic spline with knots at the 5th, 35th, 65th and 95th percentiles. Models were centered at the 10 ug/mL of 1,5-AG. Display of the data was truncated at the 95th percentiles. The gray shaded areas are 95% confidence intervals. Frequency histograms (light gray bars) are shown for each biomarker, and are truncated at the 95th percentiles.

Figure 2. Mean and 95% confidence interval of 1,5-anhydroglucitol baseline and year-1, by glucose treatment arm and blood pressure treatment arm.

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