1,5-Anhydroglucitol: A Novel Biomarker of Adherence to Sodium–Glucose Cotransporter 2 Inhibitors

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In 2003, the U.S. Food and Drug Administration cleared the biomarker 1,5-anhydroglucitol (1,5-AG) (GlycoMark) for use in intermediate-term monitoring of glucose control in patients with diabetes (1,2). Serum concentrations of 1,5-AG reflect hyperglycemia exceeding the renal threshold over the prior 1–2 weeks (3). During periods of glycosuria (>180 mg/dL), glucose and 1,5-AG compete for reabsorption in the renal tubules, resulting in increased excretion of 1,5-AG in the urine and lower concentrations of 1,5-AG in the blood (4). Thus, 1,5-AG can be used to identify individuals who are experiencing episodes of hyperglycemia.

Sodium–glucose cotransporter 2 inhibitors (SGLT2i), first approved in 2013, are a class of medications that lower blood glucose by inhibiting the reabsorption of glucose in the renal tubules and increasing glucose excretion in the urine (5). The manufacturer of the 1,5-AG assay notes that SGLT2i use substantially lowers serum concentrations of 1,5-AG, which raises the possibility that 1,5-AG could be used as a biomarker of SGLT2i use and adherence.

A blood biomarker is potentially a more objective and accurate marker of medication adherence than self-reported medication use or data on medication prescriptions. Our objective was to evaluate 1,5-AG as a biomarker of SGLT2i adherence by comparing concentrations of 1,5-AG among users and nonusers of SGLT2i in a community-based sample of adults with type 2 diabetes.

We included participants with diagnosed diabetes, defined as the use of any glucose-lowering medication, who participated in visit 6 (2016–2017), 7 (2018–2019), or 9 (2021–2022) of the Atherosclerosis Risk in Communities (ARIC) study. SGLT2i use was assessed by examination of medication bottles the participants were asked to bring to the visits. If a participant attended multiple visits, data from their most recent visit was included. If the participant reported use of SGLT2i at one visit but not at the following visit, data from the most recent visit reporting use of SGLT2i was included.

Serum 1,5-AG was measured using the GlycoMark assay (Precision Diabetes, Inc.). We examined characteristics of the study population and summary statistics according to SGLT2i use. We used frequency histograms and kernel density plots to examine the distribution of 1,5-AG by use of SGLT2i.

Among 937 participants with diabetes who were taking at least one glucose-lowering medication (mean age 81 years, 55% female, 62% White), 4.3% (n = 40) were using SGLT2i. Those on SGLT2i were more likely to be male than those using other glucose-lowering medications (63% vs. 44%). Among SGLT2i users, 12.5% (n = 5) were not using any additional glucose-lowering medications, 37.5% (n = 15) were using a sulfonylurea, and 50% (n = 20) were using other glucose-lowering medications.

Mean serum 1,5-AG was 2.6 μg/mL among SGLT2i users compared with 12.0 μg/mL (78% difference) among users of other glucose-lowering medications (Fig. 1). Among SGLT2i users, 93% had 1,5-AG <6 μg/mL compared with 24% in nonusers. Additionally, among SGLT2i users, 12.5% had 1,5-AG >3 μg/mL compared with 91.3% among users of other glucose-lowering medications.

In older adults with diabetes, we observed very low blood concentrations of 1,5-AG among SGLT2i users compared with nonusers.

Our results are consistent with a post hoc analysis of a phase 3 trial of canagliflozin in 40 patients with type 2 diabetes that found that after 26 weeks, 1,5-AG was significantly lowered by canagliflozin use but not by placebo. The mean change in 1,5-AG in the canagliflozin arm was −5.7 μg/mL, and the mean change in the placebo arm was 1.0 μg/mL (difference of −6.8 μg/mL) (5). These findings and ours support the notion that SGLT2i use affects the concentration of 1,5-AG.

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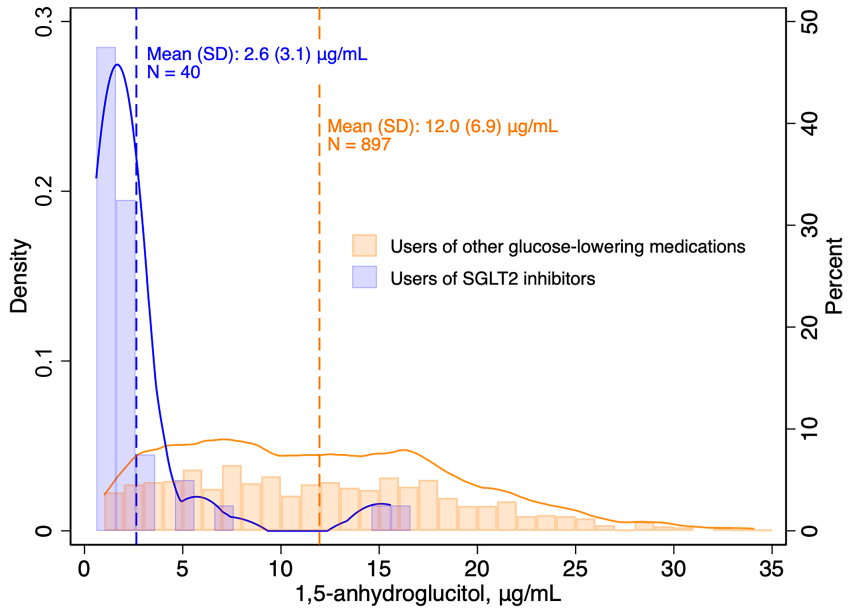

Figure 1—Distribution of 1,5-AG according to use of SGLT2i in the ARIC study (2016–2022).

Our study is the largest investigation to date to assess concentrations of 1,5-AG in people using SGLT2i. Limitations of our study include that we only had a single measure of 1,5-AG, we were unable to compare the concentrations of 1,5-AG before and after initiation of SGLT2i, and there may have been some misclassification of SGLT2i use.

The very low blood concentrations of 1,5-AG in users of SGLT2i in this community-based cohort support that 1,5-AG may be a useful biomarker of SGLT2i use. Our findings suggest that 1,5-AG may be useful in clinical research and trials as a marker of adherence. Larger studies with measurements of 1,5-AG before and after initiation of SGLT2i are needed to confirm our findings.

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