Association of a Biomarker of Glucose Peaks, 1,5-Anhydroglucitol, With Subclinical Cardiovascular Disease

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OBJECTIVE
1,5-Anhydroglucitol (1,5-AG) is a biomarker of glucose peaks and has been associated with clinical cardiovascular disease. However, the association between 1,5-AG and subclinical cardiovascular disease is unknown. We investigated the association of 1,5-AG with subclinical myocardial damage (assessed by high-sensitivity cardiac troponin T [hs-cTnT]) and atherosclerosis (assessed by carotid intima-media thickness [CIMT] and carotid plaque).

RESEARCH DESIGN AND METHODS
We measured 1,5-AG, hs-cTnT, CIMT, and carotid plaque among 10,072 people without diabetes and 681 with diabetes who attended the second examination of the Atherosclerosis Risk in Communities (ARIC) Study (baseline, 1990–1992). We used Poisson regression to characterize the associations between 1,5-AG and prevalent elevated hs-cTnT, thick CIMT, or carotid plaque. Among 9,145 people with a second hs-cTnT measurement 6 years later, we used multinomial logistic regression to assess associations with incident elevation in hs-cTnT.

RESULTS
We found that in people with diabetes, lower 1,5-AG (<6 μg/mL) was cross-sectionally associated with elevated hs-cTnT (prevalence ratio 2.06, 95% CI 1.23–3.46) compared with higher 1,5-AG (≥10 μg/mL). Associations in people without diabetes and with thick CIMT or the presence of carotid plaque were less robust. Low 1,5-AG was prospectively associated with the 6-year incident elevation in hs-cTnT (relative risk 2.90, 95% CI 1.23–6.85) in people with diabetes. All associations were strongly attenuated with further adjustment for HbA1c.

CONCLUSIONS
In people with diabetes, 1,5-AG was associated with subclinical cardiovascular disease, particularly chronic subclinical myocardial damage. Nonetheless, whether observed associations are truly independent of average glycemia is unclear.

1,5-Anhydroglucitol (1,5-AG) is a dietary monosaccharide that resembles glucose structurally (1,2). Plasma 1,5-AG competes with glucose for reabsorption in the renal tubules and demonstrates stable concentrations when its intake and excretion are balanced. However, in the setting of hyperglycemia, high amounts of glucose block tubular reabsorption of 1,5-AG, causing increased urinary losses and reduced concentrations of 1,5-AG.
serum concentrations. Thus, 1,5-AG is inversely associated with hyperglycemia, is thought to be a useful indicator of glucose peaks over the short-term (1–2 weeks) (3,4), and may provide additive information complementary to that of HbA1c (4).

Hyperglycemia and diabetes are well-known risk factors for cardiovascular disease (5–7). A growing body of evidence shows that postprandial hyperglycemia and glycemic variability are risk factors, independent of average glycemic level, for cardiovascular complications in people with diabetes (8,9). Previous studies have demonstrated an association of 1,5-AG with prevalent retinopathy and incident microvascular and macrovascular events, primarily in people with diagnosed diabetes (10–12). However, the association of 1,5-AG with subclinical cardiovascular disease is relatively uncharacterized.

New high-sensitivity cardiac troponin T (hs-cTnT) assays can detect troponin concentrations far below the conventional limit of detection of standard assays. Although cTnT is traditionally used as a highly specific marker of acute myocardial infarction, high-sensitivity assays have more recently also been used to identify chronic subclinical myocardial damage in asymptomatic individuals (13,14). Recent studies have demonstrated the independent prognostic value of new hs-cTnT assays for predicting future cardiovascular events in community-based populations (13–17).

Carotid intima-media thickness (CIMT)—measured via ultrasound imaging—is an established surrogate of atherosclerosis and is also associated with prevalent and incident cardiovascular disease (18,19). Ultrasound-detected carotid plaque is also a useful measure of subclinical disease and an independent predictor of cardiovascular outcomes (20,21). Meta-analyses show that CIMT and carotid plaque provide additional information to traditional risk factors in predicting future cardiovascular disease events in asymptomatic individuals, especially for those at intermediate risk for cardiovascular disease (22).

To the extent that 1,5-AG is a useful biomarker of glucose peaks, it may provide insight into the role of hyperglycemic excursions in the development of cardiovascular disease independent of chronic hyperglycemia. The Atherosclerosis Risk in Communities (ARIC) Study has measurements of 1,5-AG, HbA1c, hs-cTnT, CIMT, and carotid plaque all obtained at the same visit (visit 2, 1990–1992). Thus, the objective of this study was to characterize the associations of 1,5-AG with subclinical myocardial damage (assessed by hs-cTnT) and atherosclerosis (assessed by CIMT and carotid plaque) in an asymptomatic community-based population. We evaluated the potential associations of 1,5-AG with hs-cTnT, CIMT, and carotid plaque independent of traditional cardiovascular risk factors and also of HbA1c.

**RESEARCH DESIGN AND METHODS**

**Study Population**

The ARIC Study is a community-based prospective cohort that enrolled 15,792 participants from four U.S. communities (Forsyth Country, NC; Jackson, MS; Minneapolis, MN; and Washington County, MD). Details of the study design have been previously published (23). The first examination (visit 1) took place from 1987 to 1989, with three follow-up visits approximately every 3 years. More recently, a fifth visit was completed in 2011–2013. The second visit took place from 1990 to 1992 and is the baseline for the current study. There were 14,348 participants who attended visit 2. Institutional review boards at each site reviewed and approved the study protocols, and informed consent was obtained from all participants.

In the current study, we included participants who attended visit 2 and had valid measurements of key exposures, covariates, and outcomes. We excluded those with a history of clinical cardiovascular disease at or before visit 2 (n = 1,542), individuals whose race was other than white or black and African Americans in Minnesota and Washington County (n = 81), and individuals who fasted less than 8 h (n = 325) or who were missing variables of any key exposures, covariates, or outcomes (n = 1,647). Thus, for the cross-sectional analysis of elevated hs-cTnT, CIMT categories, and carotid plaque, we included 10,753 participants. A second hs-cTnT measurement was also taken at visit 4 (1996–1998), 6 years after our baseline. These additional hs-cTnT measurements permitted prospective analyses of incident elevated hs-cTnT (≥14 ng/L) at the 6-year follow-up visit.

For the prospective analyses, we excluded those participants whose hs-cTnT concentration was ≥14 ng/L at baseline (visit 2, n = 357) or who were alive at the time of visit 4 but missing hs-cTnT values at this examination (n = 1,251). Thus, for the 6-year incident elevated hs-cTnT analysis, our final analytic sample was 9,145 participants. Supplementary Figs. 1 and 2 provide more detail regarding inclusions/exclusions and timing of measurements.

**Measurement of 1,5-AG**

1,5-AG was measured with a Roche modular P800 system (GlycoMark; Roche Diagnostics Corp., Indianapolis, IN) in 2012–2013 using stored serum samples obtained from participants at baseline (visit 2, 1990–1992). Details of the GlycoMark assay have been previously described elsewhere (24). The interassay coefficient of variation (CV) was 5%. The reliability coefficient for 610 masked duplicate sample pairs was 0.99 (10). Previous studies have shown this 1,5-AG assay is reliable in long-term stored samples (24,25).

**Measurement of hs-cTnT**

hs-cTnT was measured at baseline (visit 2, 1990–1992) and visit 4 (1996–1998), using the same highly sensitive sandwich immunoassay method (Roche Elecsys T; Roche Diagnostics Corp.). hs-cTnT was measured in stored serum samples collected at visit 2 using a Roche Elecsys 10 Analyzer (Roche Diagnostics Corp.) at the University of Minnesota in 2012–2013. hs-cTnT was measured in stored plasma samples collected at visit 2 using a Roche Elecsys 10 Analyzer at Baylor College of Medicine in 2010. The measurement range of the assay is 3 mg/L to 100,000 ng/mL. For visit 2 hs-cTnT, intra-assay CVs were 2.1% at a mean hs-cTnT concentration of 26 ng/L and 1.0% at 1,990 ng/L. Interassay CVs were 6.0% at a mean hs-cTnT concentration of 25 ng/L and 3.7% at 1,940 ng/L. For visit 4 hs-cTnT, intra-assay CVs were 2.1% at a mean hs-cTnT concentration of 29 ng/L and 0.76% at 2,378 ng/L. Interassay CVs were 6.9% at mean hs-cTnT concentrations of 29 ng/L and 2.6% at 2,378 ng/L. Values ≥14 ng/L represent the 99th percentile value for a “healthy” reference group aged 20–70 years and...
are commonly used to define “elevated” levels (26). A standard calibration study was conducted to evaluate the validity of hs-cTnT across specimen type and laboratory. No significant differences were detected, and no statistical correction was indicated (27).

**Measurement of CIMT and Plaque Presence**

To assess CIMT, B-mode carotid ultrasound (Biosound 2000 II SA; Biosound, Indianapolis, IN) evaluations were completed on bilateral segments of the extracranial carotid arteries in all participants who attended the visit 2 examination. Mean far wall thickness was calculated as the mean of six far wall sites 1 cm long taken from the right and left carotid bifurcation and common and internal carotid arteries. Values for participants missing CIMT information from any carotid artery site values were imputed based on sex and race. Mean far wall CIMT was also adjusted for reader differences and measurement drift over the visit (18). The six-site mean imputed value was used in this analysis. The presence of plaque was judged by trained readers using the presence or absence of two of the following three criteria: abnormal wall thickness (defined as CIMT >1.5 mm), abnormal shape (protrusion into the lumen and loss of alignment with adjacent arterial wall boundary), and abnormal wall texture (brighter echoes than adjacent boundaries) (28,29).

**Other Variables**

Education, race, and sex were assessed at visit 1 (1987–1989), and all other covariates used in the regression models were measured at visit 2 (1990–1992). Serum glucose was measured using the hexokinase method. HbA1c was measured in stored whole-blood samples using high-performance liquid chromatography with instruments standardized to the Diabetes Control and Complications Trial assay (Tosoh A1c 2.2 and Tosoh G7) (30). Diagnosed diabetes was defined as a self-reported physician diagnosis of diabetes or current use of diabetes medication. Glomerular filtration rate was estimated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration 2009 equation (31). Left ventricular hypertrophy (LVH) was assessed with resting 12-lead electrocardiograms and defined by Cornell criteria (32). Plasma lipid concentrations, hs-CRP, BMI, and blood pressure were measured according to standardized procedures (33–35). Hypertension was defined using the mean of the second and third readings and with a cutoff for systolic blood pressure of ≥140 mmHg, a cutoff for diastolic blood pressure of ≥90 mmHg, or the use of hypertension medication. Participants reported their alcohol use and smoking status.

**Statistical Analyses**

Our main analyses were stratified by diagnosed diabetes status. We categorized 1,5-AG according to cut points recommended by the manufacturer (36) and used in prior studies (10). Participants with diagnosed diabetes were divided into three groups by 1,5-AG concentrations of <6, 6 to <10, and ≥10 μg/mL, and those without diabetes were divided into two groups by 1,5-AG concentrations of <10 and ≥10 μg/mL. Prevalent elevated hs-cTnT was defined as a concentration ≥14 ng/L at baseline (visit 2). Prevalent thick CIMT was defined using the top quartile of CIMT at the cut point of ≥0.79 mm. We used Poisson regression models with robust variances to estimate adjusted prevalence ratios (PRs) and their corresponding 95% CIs for the associations of 1,5-AG categories with prevalent elevated hs-cTnT, thick CIMT, and presence of plaque. For the prospective analysis, we used multinomial logistic regression models to estimate the adjusted cumulative incidence ratios (i.e., relative risk [RR]) of incident elevated hs-cTnT or cardiovascular events and deaths during the 6-year follow-up period. In participants with diabetes, we also examined the association of 1,5-AG categories with each of the three outcomes after stratification by glycemic control (i.e., HbA1c level <7% or ≥7%). To characterize the continuous associations of 1,5-AG in the overall population with the various outcomes, restricted cubic splines were fit with five knots placed at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles (37). A 1,5-AG value at the 10th percentile (10.1 μg/mL) was used as the reference point in all spline models. We also conducted a sensitivity analysis using Poisson regression models to estimate RR in the prospective analysis in a sample with additional exclusions for 344 participants who died between visit 2 and visit 4 and 786 nonfatal cardiovascular disease outcomes before visit 4 (Supplementary Fig. 1).

We evaluated three models for each outcome. Model 1 was adjusted for age, sex, and race-center (whites, Washington County; whites, Minneapolis; blacks, Jackson; blacks, Forsyth County; or whites, Forsyth County). Model 2 was adjusted for all variables in model 1 plus lipids (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), BMI, estimated glomerular filtration rate (eGFR), systolic blood pressure, blood pressure–lowering medication use, current drinking, current smoking, lipid–lowering medication use, CRP, and LVH. Model 3 was adjusted all variables in model 2 plus HbA1c. We tested for interactions by sex and race. Analyses were conducted using Stata/SE 13.0 software (StataCorp LP).

**RESULTS**

Baseline characteristics of the study population according to categories of 1,5-AG in participants with and without diagnosed diabetes are reported in Table 1. In general, baseline risk factor associations for 1,5-AG were similar to what is known about risk factors for hyperglycemia in diabetes. Black race, higher BMI, lower HDL cholesterol, and higher triglycerides were all associated with lower baseline concentrations of 1,5-AG in participants with or without diabetes. The substantially different distributions of 1,5-AG in individuals with and without diagnosed diabetes are evident from the sample sizes presented in Table 1 and the frequency histograms shown in Fig. 1.

In cross-sectional analyses, low concentrations of 1,5-AG were significantly associated with prevalent elevations of hs-cTnT in individuals both with and without diagnosed diabetes (Table 2). The highest prevalence of elevated hs-cTnT was in people with diagnosed diabetes and 1,5-AG of <6 μg/mL. The associations were attenuated but remained significant after adjustment for major risk factors. In individuals without diagnosed diabetes, the significant associations remained even after adjustment for HbA1c. In those with diagnosed diabetes, the PRs for hs-cTnT remained elevated but were no longer statistically significant after adjustment for HbA1c (model 3). In the overall population,
there was a robust continuous association between 1,5-AG and prevalent elevated hs-cTnT but only at low 1,5-AG values. Indeed, the association appeared strongly linear at 1,5-AG values of less than ~15 mg/mL (Fig. 1A).

Participants without diagnosed diabetes and low 1,5-AG were significantly more likely to have thick CIMT compared with individuals with high 1,5-AG (~10 μg/mL) before further adjustment for HbA1c. However, those participants with 1,5-AG levels between 6 and 10 μg/mL had the highest prevalence of carotid atherosclerosis (CIMT ≥0.79 mm) (PR 1.31, 95% CI 0.98–1.75) (model 2, Table 2), and no clear dose-response relationship between 1,5-AG categories and thick CIMT was observed.

In analyses in participants with diagnosed diabetes and stratified by HbA1c level (<7% or ≥7%), we observed that the association of low 1,5-AG with elevated hs-cTnT was limited to those individuals with HbA1c ≥7% (Supplementary Table 2), although the number of events in people with HbA1c <7% was extremely limited (n = 15 persons with hs-cTnT ≥14 ng/L). Conversely, for thick CIMT and plaque, the associations were null in individuals with HbA1c ≥7%, but statistically significant positive associations were observed in those with HbA1c <7% (model 2, Supplementary Table 1).

In the continuous analysis in the overall population, there was evidence for a significant but moderate association of 1,5-AG with thick CIMT, but only at low values of 1,5-AG (Fig. 1B). Similarly, participants with diagnosed diabetes and 1,5-AG 6 to <10 μg/mL had a higher prevalence of plaque than those with 1,5-AG ≥10 μg/mL (Table 2) and no clear dose-response relationship across categories. The PRs for carotid plaque remained elevated even after adjustment for HbA1c (model 3, Table 2) in participants with diabetes and 1,5-AG levels between 6 and 10 μg/mL. We did not observe strong evidence for a robust dose-response association of 1,5-AG with plaque presence (Table 2 and Fig. 1C).

In our prospective analyses of 9,145 individuals with hs-cTnT <14 ng/L at baseline, 477 cases of incident elevated hs-cTnT were detected at the 6-year follow-up visit (visit 4). There were also 344 deaths and 786 nonfatal cardiovascular events between visits 2 and 4. In our multinomial regression model in participants with diagnosed diabetes, we observed robust independent

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Table 1—Characteristics overall and by categories of 1,5-AG in individuals with and without diagnosed diabetes at baseline in ARIC study participants with no history of cardiovascular disease (N = 10,753)

| Characteristic                        | Overall     | No diagnosed diabetes (n = 10,072) | Diagnosed diabetes (n = 681) |
|---------------------------------------|-------------|-----------------------------------|-----------------------------|
|                                       | N = 10,753 | n = 9,448                          | n = 264                     |
|                                       | N = 10,753 | n = 9,448                          | n = 264                     |
| 1,5-AG (μg/mL)                        | 18.3 (14.4, 22.0) | 19.0 (15.7, 22.5) | 7.4 (5.5, 8.9) |
| 1,5-AG (μg/mL) (min, max)             | (0.5, 49.4) | (0.6, 9.9) | (10.1, 33.9) |
| HbA1c (%)                             | 5.6 (1.0) | 6.1 (1.6) | 6.1 (0.8) |
| Fasting glucose (mmol/L)              | 6.1 (1.8) | 5.7 (0.7) | 6.8 (2.8) |
| Age (years)                           | 56.7 (5.7) | 56.5 (5.6) | 57.3 (6.1) |
| Hypertension                          | 34.4       | 32.7     | 36.4     |
| Female                                | 57.6       | 57.2     | 63.9     |
| Black                                 | 21.6       | 20.0     | 27.1     |
| Current smoker                        | 21.2       | 21.6     | 17.3     |
| Current drinker                       | 58.6       | 60.2     | 57.1     |
| LVH                                   | 1.9        | 1.7      | 3.4      |
| BMI ≥30 kg/m²                         | 26.5       | 24.8     | 29.3     |
| hs-CRP ≥3 mg/dL                       | 36.6       | 34.8     | 39.4     |
| Lipid medication use                  | 5.2        | 4.9      | 4.5      |
| Education                              |            |          |          |
| Less than high school                 | 19.0       | 18.1     | 18.3     |
| High school or equivalent             | 42.3       | 42.6     | 40.7     |
| College or above                      | 38.5       | 39.1     | 40.9     |
| LDL cholesterol (mmol/L)              | 3.4 (0.9)  | 3.4 (0.9) | 3.5 (1.0) |
| HDL cholesterol (mmol/L)              | 1.2 (1.0, 1.6) | 1.2 (1.0, 1.5) | 1.2 (1.0, 1.5) |
| Triglycerides (mmol/L)                | 1.3 (0.9, 1.8) | 1.3 (0.9, 1.8) | 1.3 (0.9, 1.8) |
| Total cholesterol (mmol/L)            | 5.4 (1.0)  | 5.4 (1.1) | 5.4 (1.1) |
| eGFR (mL/min/1.73 m²)                 | 96.8 (14.6) | 96.7 (14.1) | 96.7 (16.5) |
| eGFR <60 mL/min/1.73 m²               | 1.3        | 1.1      | 2.7      |
| Elevated hs-cTnT (≥14 ng/L)           | 3.3        | 2.6      | 6.1      |
| Measured hs-cTnT (≥3 ng/L)            | 32.8       | 31.3     | 35.9     |
| Thick CIMT (≥0.79 mm)                 | 21.6       | 20.4     | 25.2     |
| Plaque presence                       | 31.5       | 30.8     | 32.5     |

Continuous variables are reported as mean (SD) or median (25th percentile, 75th percentile), and categorical variables are reported as a percentage, unless otherwise noted.
associations of baseline 1,5-AG categories with 6-year incident elevation in hs-cTnT or cardiovascular events and deaths before further adjustment for HbA1c (Table 3). With further adjustment for HbA1c, the associations were no longer statistically significant (model 3).

No significant associations of low 1,5-AG with incident elevated hs-cTnT or cardiovascular events and deaths were observed in participants without diagnosed diabetes before or after adjustment. In analyses of participants with diagnosed diabetes and stratified by HbA1c level (<7% or ≥7%) at baseline, the associations with incident elevated hs-cTnT were largely limited to those with HbA1c ≥7%, although power was limited owing to the small numbers of events within groups (Supplementary Table 2).

When 1,5-AG was modeled continuously, a strong association with incident elevated hs-cTnT was observed, but only at low 1,5-AG concentrations, consistent with the cross-sectional results (Fig. 1D). Our sensitivity analyses of 8,015 participants with no prevalent or incident cardiovascular disease during the 6-year follow-up period found similar patterns of association of baseline 1,5-AG with incident elevation in hs-cTnT (Supplementary Table 1).

We did not observe statistically significant interactions by race or sex for 1,5-AG categories with any of the outcomes in participants with or without diabetes.

CONCLUSIONS

Results from the current study showed that 1,5-AG was associated with subclinical cardiovascular disease, as assessed by elevated hs-cTnT, CIMT, and presence of carotid plaque, especially in participants with diabetes and (very low) levels of 1,5-AG. We further observed that 1,5-AG was also associated with incident elevations in hs-cTnT during a 6-year follow-up period in participants with diabetes before adjustment for HbA1c.

Prior studies have shown 1,5-AG is associated with clinical complications of diabetes in cross-sectional and prospective settings (9–11). In the current study, associations of 1,5-AG with subclinical myocardial damage, as assessed
by hs-cTnT, were generally stronger and more robust than the associations observed for measures of atherosclerosis (CIMT and carotid plaque). We also observed that, for hs-cTnT, the signal was strongest among participants with diabetes and poor glycemic control (i.e., HbA1c ≥7%); whereas, associations for thick CIMT and plaque were null in participants with HbA1c ≥7% but significant in those with HbA1c <7%. These divergent results may reflect the differing pathways by which hyperglycemic states contribute to atherosclerotic cardiovascular disease (CIMT and plaque) compared with subclinical damage to the heart (hs-cTnT). Nonetheless, HbA1c is a marker of sustained (ambient) hyperglycemia, and 1,5-AG is thought to be a marker of glucose peaks; yet, these two parameters are inextricably linked and cannot be separated in a precise manner. In people with HbA1c <7%, low concentrations of 1,5-AG may largely reflect postprandial glucose excursions. In those with higher HbA1c levels (e.g., HbA1c ≥7%), low concentrations of 1,5-AG more likely reflect sustained basal hyperglycemia in addition to glucose peaks.

Our results extend previous findings and support a possible harmful effect of hyperglycemic peaks on the myocardium, or perhaps on the microvascular supply to the myocardium, and possibly a role in the development of atherosclerosis. Nonetheless, the observed associations were largely nonsignificant after further adjustment for Hba1c. The lack of significant associations after adjustment for Hba1c suggests that glucose peaks may not have substantial clinical significance beyond average glycaemia, although our effect estimates at very low levels of 1,5-AG were imprecise (as reflected in the wide 95% CIs), suggesting that our study may have been underpowered to detect an association independent of Hba1c. Indeed, for prevalent elevated hs-cTnT, the PRs among participants without diabetes remained elevated even after adjustment for Hba1c, whereas in the prospective analysis, the associations of 1,5-AG with the 6-year risk of incident elevated hs-cTnT or cardiovascular events were nonsignificant after adjustment for Hba1c. For context, a prior study of ARIC participants from our group with longer follow-up (20 years) and more than 1,000 cardiovascular events demonstrated that 1,5-AG adds prognostic value for future vascular outcomes even after accounting for Hba1c or fasting glucose (10), supporting the contention that the present analysis, with only 6 years of follow-up and much fewer events, may have simply been underpowered to detect a moderate independent association.

Prior studies have suggested that hyperglycemic variability may be an independent risk factor for macrovascular and microvascular complications in people with diabetes (38). The current study extends these findings by showing that low 1,5-AG concentrations (i.e., <15 µg/mL) were associated with measures of subclinical cardiovascular disease and a higher risk for future subclinical myocardial damage. As can be seen in our analyses of the overall population, the associations were clearly driven by low concentrations of 1,5-AG regardless of diabetes diagnostic status.

It is important to note that this study had several limitations. First, we had only two measurements of hs-cTnT, 6 years apart, to characterize progression of subclinical myocardial damage. Second, we relied on a single measurement of 1,5-AG, although 1,5-AG has been shown to track well within individuals over time (39). Third, the presence of plaque was measured subjectively (28,29). Despite rigorous adjustment for potentially confounding factors, we cannot eliminate the possibility of residual confounding in this observational study. Fourth, contemporaneous oral glucose tolerance tests were not available for comparison with 1,5-AG in this study.

Strengths of this study included the large community-based sample and rigorous measurement of traditional cardiovascular and diabetes risk factors. Additional studies with comparisons to oral glucose tolerance tests will be useful to further understand the potential clinical utility of 1,5-AG.

In summary, we found that 1,5-AG was associated with prevalent and incident subclinical cardiovascular disease

| Table 2—Adjusted PRs (95% CIs) for elevated hs-cTnT, thick CIMT, and presence of plaque by categories of 1,5-AG in participants with and without diagnosed diabetes and no history of clinical cardiovascular disease at baseline (1990–1992) (N = 10,753) |
|-----------------|-----------------|-----------------|-----------------|
|                | n/N             | PR (95% CI)     | PR (95% CI)     | PR (95% CI)     |
| Elevated hs-cTnT (≥14 ng/L) |                 |                 |                 |
| No diagnosis of diabetes |                 |                 |                 |
| 1,5-AG ≥10 µg/mL | 224/9,448       | 1 (reference)   | 1 (reference)   | 1 (reference)   |
| 1,5-AG <10 µg/mL | 38/624          | 2.24 (1.62–3.10)| 1.98 (1.43–2.73)| 1.93 (1.33–2.81)|
| Diagnosed diabetes |                 |                 |                 |
| 1,5-AG ≥10 µg/mL | 18/264          | 1 (reference)   | 1 (reference)   | 1 (reference)   |
| 1,5-AG <10 µg/mL | 9/91            | 1.24 (0.59–2.60)| 1.51 (0.73–3.13)| 1.40 (0.67–2.95)|
| 1,5-AG <10 µg/mL | 48/326          | 2.04 (1.23–3.39)| 2.06 (1.23–3.46)| 1.62 (0.81–3.25)|
| Thick CIMT (≥0.79 mm) |                 |                 |                 |
| No diagnosis of diabetes |                 |                 |                 |
| 1,5-AG ≥10 µg/mL | 1,923/9,448     | 1 (reference)   | 1 (reference)   | 1 (reference)   |
| 1,5-AG <10 µg/mL | 157/624         | 1.19 (1.04–1.37)| 1.16 (1.01–1.33)| 1.13 (0.97–1.31)|
| Diagnosed diabetes |                 |                 |                 |
| 1,5-AG ≥10 µg/mL | 80/264          | 1 (reference)   | 1 (reference)   | 1 (reference)   |
| 1,5-AG <10 µg/mL | 37/91           | 1.27 (0.94–1.71)| 1.31 (0.98–1.75)| 1.25 (0.93–1.70)|
| 1,5-AG <10 µg/mL | 120/326         | 1.23 (0.98–1.54)| 1.24 (0.99–1.55)| 1.06 (0.76–1.48)|
| Plaque |                 |                 |                 |
| No diagnosis of diabetes |                 |                 |                 |
| 1,5-AG ≥10 µg/mL | 2,907/9,448     | 1 (reference)   | 1 (reference)   | 1 (reference)   |
| 1,5-AG <10 µg/mL | 203/624         | 1.04 (0.93–1.16)| 1.05 (0.94–1.17)| 1.04 (0.92–1.17)|
| Diagnosed diabetes |                 |                 |                 |
| 1,5-AG ≥10 µg/mL | 100/624         | 1 (reference)   | 1 (reference)   | 1 (reference)   |
| 1,5-AG <10 µg/mL | 45/91           | 1.24 (0.96–1.61)| 1.28 (1.00–1.65)| 1.30 (1.00–1.69)|
| 1,5-AG <10 µg/mL | 129/326         | 1.09 (0.89–1.33)| 1.11 (0.91–1.35)| 1.17 (0.87–1.57)|

Model 1: Age, sex, and race-center. Model 2: Variables in model 1 plus lipids (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides), BMI, eGFR, systolic blood pressure, blood pressure-lowering medication use, current drinking, current smoking, lipid-lowering medication use, CRP, and LVH. Model 3: Variables in model 2 plus Hba1c.
in a community-based population of individuals with diabetes. Our study provides evidence for a potentially deleterious effect of glucose peaks on the development of vascular disease, but whether this association is truly independent of average glycemia is unclear. Further studies are needed to understand whether 1,5-AG may be useful in certain clinical settings and add complementary information to traditional measures of hyperglycemia.

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