Association of 1,5-anhydroglucitol with cardiovascular disease and mortality

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ABSTRACT (unstructured, 200 word limit)

In diabetes, low concentrations of the biomarker 1,5-anhydroglucitol (1,5-AG) reflect hyperglycemic excursions over the prior 1-2 weeks. To the extent that hyperglycemic excursions are important in atherogenesis, 1,5-AG may provide independent information regarding cardiovascular risk. Nonetheless, few studies have evaluated associations of 1,5-AG with long-term cardiovascular outcomes in a population-based setting. We measured 1,5-AG in 11,106 participants in the Atherosclerosis Risk in Communities (ARIC) Study without cardiovascular disease at baseline (1990-1992) and examined prospective associations with coronary heart disease (n=1159 events), ischemic stroke (n=637), heart failure (n=1553), and death (n=3120) over 20 years of follow-up. Cox proportional hazards models were adjusted for demographic and cardiovascular risk factors. Compared to persons with 1,5-AG ≥6 ug/mL and no history of diabetes, persons with diabetes and 1,5-AG <6.0 ug/mL had an increased risk of coronary heart disease (HR 3.85, 95%CI 3.11-4.78), stroke (HR 3.48, 95%CI 2.66-4.55), heart failure (HR 3.50, 95%CI 2.93-4.17), and death (HR 2.44, 95%CI 2.11-2.83). There was a threshold effect, with little evidence for associations at "non-diabetic" concentrations of 1,5-AG (e.g., >10 ug/mL). Associations remained but were attenuated with additional adjustment for fasting glucose or HbA1c. These data add to the growing evidence for the prognostic value of 1,5-AG for long-term complications in the setting of diabetes.

Hemoglobin A1c (HbA1c) reflects glycemic exposure over the past 2-3 months, is the standard measure used for the clinical monitoring of glucose control, and is also recommended for diagnosis of diabetes [1]. 1,5-anhydroglucitol (1,5-AG) or 1-deoxyglucose is a monosaccharide originating primarily from dietary sources and is an alternative biomarker of hyperglycemia. In the normal state, 1,5-AG is typically present at high but constant concentrations in the blood. It is freely filtered by the glomeruli and reabsorbed in the renal tubule with a small amount, corresponding to dietary intake, excreted in the urine. In the setting of hyperglycemia (specifically, when blood glucose exceeds the renal threshold of ~160-180 mg/dL), high amounts of glucose block renal tubular reabsorption of 1,5-AG, causing serum 1,5-AG concentrations to fall. Therefore, low serum 1,5-AG can serve as a marker of short-term hyperglycemia and concentrations are thought to reflect hyperglycemic episodes over an approximate 1-2 week period [2-4]. Appealingly, 1,5-AG is a non-fasting test that may capture additional information on glycemic excursions that are not reflected in HbA1c [5]. A growing literature provides evidence that 1,5-AG may provide a useful complement to HbA1c measurements in some settings [5-14], especially when seeking to characterize short-term glycemic variability that may not be reflected in standard metrics of glycemia.

Previous studies suggest that post-prandial glycemic excursions may be an independent risk factor for cardiovascular disease [15-21]; although this contention is controversial [22-25]. Chronic exposure to post-prandial elevations in glucose is hypothesized to induce endothelial dysfunction and contribute to the development of atherosclerosis [26, 27]. There is some evidence from epidemiologic studies that 2-hour glucose measurements may be more strongly associated with cardiovascular events compared to fasting glucose [24, 28], but this finding has been inconsistent [29].

Among persons without a history of diabetes, HbA1c is more strongly associated with vascular outcomes as compared to fasting glucose [30-32]. This may be partly reflect the lower within-person variability of HbA1c compared to fasting glucose but may also be a function of the importance of non-fasting glucose in the development of vascular complications of diabetes [33].

To the extent that hyperglycemic excursions are important in atherogenesis, 1,5-AG may provide independent information regarding cardiovascular risk. Nonetheless, few studies have evaluated the associations of 1,5-AG with long-term cardiovascular outcomes in a population-based setting. We have previously shown that 1,5-AG is strongly associated with important microvascular outcomes (kidney disease and retinopathy), particularly in persons with diabetes and even after adjustment for HbA1c [34]. The association of 1,5-AG with incident cardiovascular outcomes is uncharacterized. In this study, our aim was to characterize the independent association 1,5-AG with future risk for coronary heart disease, heart failure, stroke, and all cause mortality in a community-based population.

METHODS

Study Population

The ARIC Study is a community-based prospective cohort of over 15,000 participants sampled from four U.S. communities. The first clinic examinations (visit 1) took place from 1987 to 1989, with three follow-up visits approximately every three years [35]. A fifth visit was recently completed (2011-2013). The second clinic examination (visit 2) took place from 1990 to 1992 and is the baseline for the present study. There were 14,348 participants who attended visit 2. Institutional review boards at all institutions reviewed the study and informed consent was obtained from all participants.

In the present study, we excluded all persons whose race/ethnicity was recorded as other than white or black (N=91), who were fasting less than 8 hours (N=446), who had a history of coronary heart disease, stroke, or heart failure (N=1391), or who were missing variables of interest (N=1314), for a final analytic sample of 11,106 (762 persons with diagnosed diabetes and 10,344 persons without a diagnosis of diabetes). Persons with diagnosed diabetes were classified on the basis of a self-reported history of physician-diagnosed diabetes or current glucose-lowering medication use.

Measurement of 1,5-AG

1,5-AG (GlycoMark, Wiston-Salem, NC) was measured using a Roche Modular P800 system in 2012-2013 in stored serum specimens obtained at ARIC visit 2. The inter-assay CV was 5%. The reliability coefficient for N=610 masked duplicate specimen pairs was 0.99. Previous studies have shown this 1,5-AG assay to be highly reliable even in long-term stored samples [8, 36].

Other variables

Serum glucose was measured using the hexokinase method. HbA1c was measured in whole blood samples using HPLC with instruments standardized to the Diabetes Control and Complications Trial assay (Tosoh A1c 2.2. Plus Glycohemoglobin and Tosoh G7 analyzers) [37]. Plasma lipid concentrations, body mass index (kg/m^2), and blood pressure were measured using standard ARIC protocols [38-42]. Serum creatinine was measured using a modified kinetic Jaffé method. Estimated glomerular filtration rate was calculated from serum creatinine using the 2009 CKD-Epidemiology Collaboration (CKD-EPI) equation[43]. Hypertension was defined as the mean of the second and third readings at the visit (with cutoff for systolic blood pressure of 140 mmHg

or higher and/or a cutoff for diastolic blood pressure of 90 mmHg or higher) or the use of hypertension medication. Education, alcohol use, and smoking status were self-reported. Physical activity was assessed using the Baecke's index, a measure of habitual leisure (sport and exercise related) activity[44].

Assessment of coronary heart disease, stroke, heart failure, and all-cause mortality

The ascertainment of deaths and classification of cardiovascular events are detailed elsewhere [45, 46]. Briefly, deaths and potential cardiovascular hospitalizations were reported annually by participants (or proxy) and also identified through community-wide hospital surveillance, and linkage to state and national death indexes. Trained personnel abstracted hospital records related to possible cardiovascular events and these outcomes are adjudicated by a panel of experts. Silent myocardial infarction, as detected by means of electrocardiography during the visits, were also identified and recorded. We defined newly diagnosed coronary heart disease as a definite or probable myocardial infarction, a death from coronary heart disease, or electrocardiographic evidence of a silent myocardial infarction detected at one of the follow-up visits. We also examined definite or probable ischemic stroke (adjudicated). Incident heart failure was defined as the first heart failure hospitalization identified by ICD-9 codes of 428.X in any position on the hospital discharge list or a death certificate with death from heart failure in any position. Follow-up data for all cardiovascular events were available up to January 1, 2013.

Statistical Analyses

Baseline characteristics of the study population were compared across categories of 1,5-AG in persons with and without a history of diagnosed diabetes. Low serum concentrations of 1,5-AG

reflect hyperglycemic excursions (inverse association with serum glucose); a 1,5-AG concentration of 6 ug/mL or less is thought to reflect high peaks of glucose (>~200 mg/dl) over the past 1-2 weeks whereas a concentration of 10 or more is thought to reflect the absence of recent, significant hyperglycemia (glucose peaks <~180 mg/dl) [5]. We divided the populations of persons with and without diabetes into two groups based on a cut-point of 6 ug/mL. Those persons with no history of diabetes and 1,5-AG ≥6 ug/mL served as the common reference group in our overall categorical analysis. We also conducted analyses stratified by diabetes status.

To characterize the associations of 1,5-AG with incident cardiovascular outcomes and all-cause mortality, we used Cox proportional hazards models to estimate hazard ratios and their corresponding 95% confidence intervals. We verified that the proportional hazards assumption was met using log-log plots. In analyses with 1,5-AG modeled categorically, p-values-for-trends were calculated by modeling the category medians as a continuous variable. To characterize the shape of the continuous association of 1,5-AG at baseline with each endpoint, we fit linear and restricted cubic splines, using the 10^{th} percentile (1,5-AG = 10 ug/L) as the reference point and with knots placed at the 5^{th}, 35^{th}, 65^{th}, and 95^{th} percentiles.[47]

We constructed 4 models for each of the outcomes. Model 1 was adjusted for age, sex, race-field center (white participants, Minnesota, Maryland, and North Carolina; black participants, Mississippi and North Carolina). Model 2 was adjusted for all variables in Model 1 plus LDL-cholesterol (mg/dL), HDL-cholesterol (mg/dL), triglycerides (mg/dL), body mass index (kg/m^2), waist-to-hip ratio, systolic blood pressure (mmHg), blood pressure-lowering medication use (yes, no), education (less than high school, high school or equivalent, more than high school), drinking status (current, former, never), smoking status (current, former, never), physical activity index, and glomerular filtration rate (mL/min per 1.73 m^2). Model 3 was

adjusted for all variables in Model 2 plus HbA1c (%). Model 4 was adjusted for all variables in Model 2 plus fasting glucose (mg/dL). We tested for multiplicative interactions by age, sex, and race. All statistical analyses were conducting using Stata SE version 13.1.

RESULTS

In persons with diagnosed diabetes (n = 762), almost half (49%) of participants had low 1,5-AG (<6 ug/mL)—consistent with recent peaks of glucose of ~>200 mg/dL; 62% had 1,5-AG <10 ug/mL. In persons without a history of diagnosed diabetes (n = 10,344), just less than 2% (n=203) of participants had concentrations <6 ug/mL. Categories of 1,5-AG were strongly and inversely associated with traditional diabetes risk factors (**Table 1**). Among persons with a diagnosis of diabetes, those persons in the low 1,5-AG category (<6 ug/mL) had higher mean HbA1c and fasting glucose values; were more likely to be obese or have hypertension; and had a poorer lipid profile.

The substantially different distributions of 1,5-AG in persons with and without a diagnosis of diabetes are shown in the histograms (**Figure 1**). In persons without diagnosed diabetes (the majority of participants in this study), the distribution of 1,5-AG is roughly normal (solid grey histogram). In persons with diagnosed diabetes, the distribution of 1,5-AG was non-normal and highly right-skewed (solid line transparent histogram). During a median of over 21 years of follow-up, there were 1159 coronary heart disease events, 637 ischemic stroke events, 1,533 heart failure events, and 3,120 deaths. Low values of 1,5-AG (~<10 ug/mL) were strongly associated with all vascular outcomes and death (**Figure 1**). Results were similar when 1,5-AG was modeled using linear splines (**eFigure 1**). We observed a threshold effect, with little evidence of risk associations at ("non-diabetic") 1,5-AG concentrations of ~10 to 15 ug/mL or

higher. Indeed, in the categorical analyses, the associations with the clinical outcomes were largely confined to persons with diagnosed diabetes (**Table 2 and eTable 1**). Among persons with diagnosed diabetes, those persons with 1,5-AG <6 ug/mL had a significantly increased risk of coronary heart disease, ischemic stroke, heart failure, or death, even after adjustment for traditional diabetes and cardiovascular risk factors (**Table 2, Model 2**). The associations of low 1,5-AG with the coronary heart disease, heart failure, and death were attenuated but remained significant even after further adjustment for HbA1c (**Table 2, Model 3**) or fasting glucose (**Table 2, Model 4**). The association with ischemic stroke remained significant after additional adjustment for fasting glucose (**Table 2, Model 4**) but not HbA1c (**Table 2, Model 3**). We did not observe interactions by sex or race for any of the outcomes, but there was some evidence for modest effect modification by age for risk of heart failure and death (**eTable 2**). The associations of 1,5-AG with heart failure and death were somewhat stronger in younger persons (<57 years of age) compared to older (≥ 57 years of age).

CONCLUSIONS

We found that 1,5-AG, a putative biomarker of hyperglycemic excursions over the prior 1-2 weeks, was strongly associated with cardiovascular outcomes and mortality in the setting of diabetes, even after adjustment for baseline fasting glucose or HbA1c. These data help inform a long-standing debate regarding the independent role of post-prandial hyperglycemia as a risk factor for cardiovascular outcomes[17, 48, 49].

Numerous studies have compared fasting glucose and 2-hour glucose as risk factors for cardiovascular events and debated their relative importance. Initial epidemiologic studies suggested that 2-hour glucose concentrations were more predictive of cardiovascular outcomes

as compared to fasting glucose, but some early reports assumed a simple linear association of hyperglycemia with vascular outcomes and few statistically compared the performance of the different biomarkers of hyperglycemia [15, 24]. However, there is robust evidence that, in many populations, the association of hyperglycemia with cardiovascular outcomes or mortality is J- or U-shaped (i.e., strongly non-linear) [30, 32, 50-55]. A recent meta-analysis which pooled data from over 73 prospective studies including almost 300,000 participants without diagnosed diabetes found J-shaped associations of 2-hour glucose, fasting glucose, and HbA1c with cardiovascular outcomes; and it directly challenged the assumption the 2-hour glucose concentrations predict cardiovascular disease better than other measures of hyperglycemia [32]. An additional difficulty in the interpretation of the epidemiologic literature relates to uncertainty about how well a single oral glucose tolerance test result captures true underlying disturbances in post-prandial glucose metabolism. HbA1c subsumes overall chronic exposure to hyperglycemia during the past ~2-3 months and thus reflects both pre- and post-prandial glucose concentrations. Recent large epidemiologic studies and meta-analyses have further demonstrated that a single HbA1c measurement outperforms either fasting or 2-hour glucose for prediction of cardiovascular outcomes and mortality [30-32]. Because 1,5-AG reflects hyperglycemic excursions over a 1-2 week period, evidence for its association with long-term outcomes adds depth to this debate.

There are few epidemiologic data linking 1,5-AG to long-term outcomes [14]. Our study adds to the evidence regarding the value of 1,5-AG as a biomarker of hyperglycemic excursion in persons with diabetes. There was a striking threshold effect, with little evidence for any associations at concentrations greater than 10 ug/mL. We found that, at very low concentrations, 1,5-AG adds prognostic value for vascular outcomes and death, even after accounting for traditional biomarkers of hyperglycemia (HbA1c or fasting glucose). Indeed, 1,5-AG may be a

useful biomarker to monitor hyperglycemic excursions, but additional studies are needed to understand its possible utility as a tool for diabetes management.

The evidence for an independent contribution of post-prandial hyperglycemia to cardiovascular risk has given rise to calls for specifically targeting postprandial hyperglycemia in diabetes management. However, the available clinical trial data informing the value of targeting post-prandial glucose to prevent diabetic complications are quite limited [56, 57]. The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP NIDDM) trial evaluated acarbose, an anti-hyperglycemic drug decreases post-prandial hyperglycemia, and demonstrated a significant reduction in cardiovascular events (a secondary endpoint in this trial) in the acarbose arm compared to placebo.[58] However, the total number of cardiovascular events was very small (n=15 in the treatment arm and n=32 in the placebo arm). The ongoing Acarbose Cardiovascular Evaluation (ACE) randomized clinical trial should help inform whether treatment with acarbose and specifically targeting post-prandial glucose concentrations can reduce the risk of cardiovascular outcomes [59].

Important limitations of our study include the reliance on a single baseline measurement of 1,5-AG and the lack of information on 2-hour post-prandial glucose; oral glucose tolerance tests were not performed at the second ARIC examination. There were also fewer ischemic stroke events as compared to the other outcomes, with corresponding lower power and less precise results for this outcome, particularly in the categorical analyses. Owing to the observational nature of the study, we are also not able to completely rule out the possibility of residual confounding. Nonetheless, this study was one of the largest community-based epidemiologic analyses of 1,5-AG to-date. We had over two decades of follow-up for the

development of adjudicated cardiovascular endpoints, heart failure hospitalizations, and deaths. Follow-up rates in the ARIC cohort are very high (>90%).

In conclusion, we found that 1,5-AG was strongly and independently associated with cardiovascular outcomes and mortality in persons with a history of diabetes. These data add to the growing evidence for the prognostic value of 1,5-AG for important long-term complications of diabetes.

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Table 1. Characteristics of Participants without a History of Cardiovascular Disease Overall and by Categories of 1,5-anhydroglucitol (1,5-AG) and Diagnosed Diabetes Status at Baseline, the ARIC Study (N=11,106)

		No Diagnosed Diabetes, N=10,344		Diagnosed Diabetes, N=762	
	Overall	1,5-anhydroglucitol ≥ 6 ug/mL	1,5-anhydroglucitol < 6 ug/mL	1,5-anhydroglucitol ≥ 6 ug/mL	1,5-anhydroglucitol < 6 ug/mL
N	11,106	10,141	203	389	373
1,5-Anhydroglucitol, ug/mL	18.2 [14.3, 21.9]	18.7 [15.2, 22.3]	4.2 [2.2,5.2]	16 [13.1, 20.1]	1.8 [1.2, 3.2]
1,5-Anhydroglucitol, ug/mL, range (min, max)	(0.6, 49.4)	(6.0, 49.4)	(0.6, 5.9)	(6.0, 33.9)	(0.6, 5.9)
HbA1c, %	5.4 [5.2, 5.8]	5.4 [5.2, 5.7]	6.3 [5.4, 8.3]	6.0 [5.6, 6.7]	9.6 [8.3, 11.0]
HbA1c, mmol/mol	36 [33, 40]	36 [33, 39]	45 [36, 67]	42 [38, 50]	81 [67, 97]
Fasting glucose, mg/dL	102 [96, 111]	101 [95, 109]	126 [100, 205]	124 [105, 147]	235 [192, 294]
Age	57 [52, 62]	57 [52, 62]	58 [53, 64]	58 [54, 64]	58 [53, 63]
Female, %	58.6	58.5	59.6	58.1	62.7
Black, %	23.4	21.9	32.5	35.7	47.7
Body mass index, kg/m^2	27.1 [24.2, 30.6]	27 [24, 30]	28 [25, 33]	29.3 [26.4, 33.6]	31.1 [27.4, 34.4]
Body mass index ≥ 30 kg/m^2, %	28.5	26.4	42.9	45.8	57.6
Hypertension, %	33.3	31.4	43.1	54.4	57.4
Education, %					
Less than high school	19.8	18.6	24.6	37.8	30.6
High school or equivalent	41.9	42.3	38.4	33.4	42.6
College or above	38.3	39.1	37.0	28.8	26.8
Current alcohol use, %	57.9	59.6	57.6	41.7	30.8
Current smoking status, %	21.4	21.6	19.7	21.9	17.4
Physical activity index	2.25 [1.75, 3.00]	2.25 [1.75, 3.00]	2.25 [1.75, 2.75]	2.25 [1.75, 2.75]	2.00 [1.75, 2.75]
LDL-cholesterol, mg/dL	131 [109, 155]	131 [109, 155]	134 [112, 166]	132 [106, 152]	137 [110, 162]
HDL-cholesterol, mg/dL	48 [39, 60]	48 [39, 61]	43 [36, 57]	44 [35, 54]	43 [35, 52]
Triglycerides, mg/dL	111 [81, 157]	109 [80, 153]	128 [94, 182]	127 [91, 179]	149 [106, 212]
eGFR ml/min per 1.73 m^2	98 [89, 106]	98 [89, 105]	100 [90, 110]	100 [88, 109]	102 [91, 113]
eGFR<60 ml/min per 1.73 m^2, %	1.37	1.18	3.45	2.83	3.75

Continuous variables are median [25th, 75th percentiles] unless otherwise noted.
Abbreviations: eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high density lipoprotein; LDL, low density lipoprotein

Table 2. Adjusted Hazard Ratios (95% Confidence Intervals) of Baseline Diabetes-Specific Categories of 1,5-Anhydroglucitol (1,5-AG) with Incident Coronary Heart Disease, Ischemic Stroke, Heart Failure, and Mortality

Outcome	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
Coronary Heart Disease				
N=1159 events				
No Diagnosis of Diabetes				
1,5-AG ≥ 6 ug/mL	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1,5-AG < 6 ug/mL	1.19 (0.77, 1.84)	1.12 (0.72, 1.72)	0.80 (0.50, 1.27)	0.93 (0.59, 1.46)
Diagnosed Diabetes				
1,5-AG ≥ 6 ug/mL	2.28 (1.81, 2.87)	1.86 (1.47, 2.36)	1.57 (1.23, 2.01)	1.66 (1.29, 2.12)
1,5-AG < 6 ug/mL	4.48 (3.66, 5.49)*	3.85 (3.11, 4.78)*	1.86 (1.27, 2.74)	2.47 (1.71, 3.57)*
p-for-trend	<0.0001	<0.0001	<0.0001	<0.0001
Ischemic Stroke				
N=637 events				
No Diagnosis of Diabetes				
1,5-AG ≥ 6 ug/mL	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1,5-AG < 6 ug/mL	2.79 (1.92, 4.06)*	2.43 (1.66, 3.55)*	1.53 (0.98, 2.39)	2.29 (1.52, 3.45)*
Diagnosed Diabetes				
1,5-AG ≥ 6 ug/mL	1.34 (0.92, 1.95)	1.12 (0.77, 1.64)	0.92 (0.63, 1.37)	1.08 (0.73, 1.60)
1,5-AG < 6 ug/mL	4.12 (3.20, 5.32)*	3.48 (2.66, 4.55)*	1.46 (0.93, 2.29)*	3.03 (1.97, 4.67)*
p-for-overall-trend	<0.0001	<0.0001	0.3923	0.0001
Heart Failure				
N=1553 events				
No Diagnosis of Diabetes				
1,5-AG ≥ 6 ug/mL	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1,5-AG < 6 ug/mL	1.15 (0.81, 1.65)	0.97 (0.68, 1.39)	0.71 (0.48, 1.05)	0.81 (0.55, 1.18)
Diagnosed Diabetes				
1,5-AG ≥ 6 ug/mL	2.02 (1.65, 2.47)	1.58 (1.29, 1.94)	1.38 (1.12, 1.71)	1.44 (1.16, 1.78)
1,5-AG < 6 ug/mL	4.37 (3.69, 5.18)*	3.50 (2.93, 4.17)*	1.91 (1.40, 2.60)*	2.44 (1.82, 3.26)*
p-for-overall-trend	<0.0001	<0.0001	<0.0001	<0.0001
All-Cause Mortality				
N=3120 events				
No Diagnosis of Diabetes				
1,5-AG ≥ 6 ug/mL	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1,5-AG < 6 ug/mL	1.47 (1.18, 1.83)*	1.39 (1.12, 1.74)*	1.18 (0.93, 1.50)	1.32 (1.05, 1.67)*
Diagnosed Diabetes				
1,5-AG ≥ 6 ug/mL	1.68 (1.44, 1.95)	1.48 (1.26, 1.72)	1.36 (1.16, 1.59)	1.43 (1.22, 1.68)
1,5-AG < 6 ug/mL	2.63 (2.28, 3.03)*	2.44 (2.11, 2.83)*	1.66 (1.30, 2.11)	2.16 (1.71, 2.72)*
p-for-overall-trend	<0.0001	<0.0001	<0.0001	<0.0001

Model 1: Age (years), race-center, sex (male, female)
Model 2: Variables in Model 1 + LDL-cholesterol (mg/dL), HDL-cholesterol (mg/dL), triglycerides (mg/dL), body mass index (kg/m^2), waist-to-hip ratio, systolic blood pressure (mmHg), blood pressure-lowering medication use (yes, no), education (less than high school, high school or equivalent, more than high school), drinking status (current, former, never), smoking status (current, former, never), physical activity index, glomerular filtration rate (mL/min per 1.73 m^2, modeled using a linear spline with a knot at the median)
Model 3: Variables in Model 2 + hemoglobin A1c (%)
Model 4: Variables in Model 2 + fasting glucose (mg/dL)
Abbreviations: 1,5-AG, 1,5-anhydroglucitol; CI, confidence interval; HR, hazard ratio.
P-values-for-overall-trend were calculated by modeling the category medians as a continuous variable.

* Indicates significant ($p<0.05$) difference between 1,5-AG categories within diabetes group (no diagnosis of diabetes or diagnosed diabetes)

Figure 1. Adjusted hazard ratios (95% CIs) for baseline 1,5-anhydroglucitol with incident coronary heart disease, ischemic stroke, heart failure, and all-cause mortality, the ARIC Study, N=11,106

[Figure in Figure1.eps]

Legend: Adjusted hazard ratios are from Cox proportional hazard regression models. 1,5-anhydroglucitol was modeled using restricted cubic splines (solid line) with knots at the 5th, 35th, 65th, and 95th percentiles, and centered at the 10th percentile. 95% confidence intervals are shown with the dashed lines. Models are adjusted for systolic blood pressure (mmHg), blood pressure-lowering medication use (yes, no), education (less than high school, high school or equivalent, more than high school), drinking status (current, former, never), smoking status (current, former, never), physical activity index, estimated glomerular filtration rate (mL/min per 1.73 m^2, modeled using a linear spline with a knot at the median). Frequency histograms are show for persons without diabetes (light gray bars) and for persons with diabetes (dark gray bars).

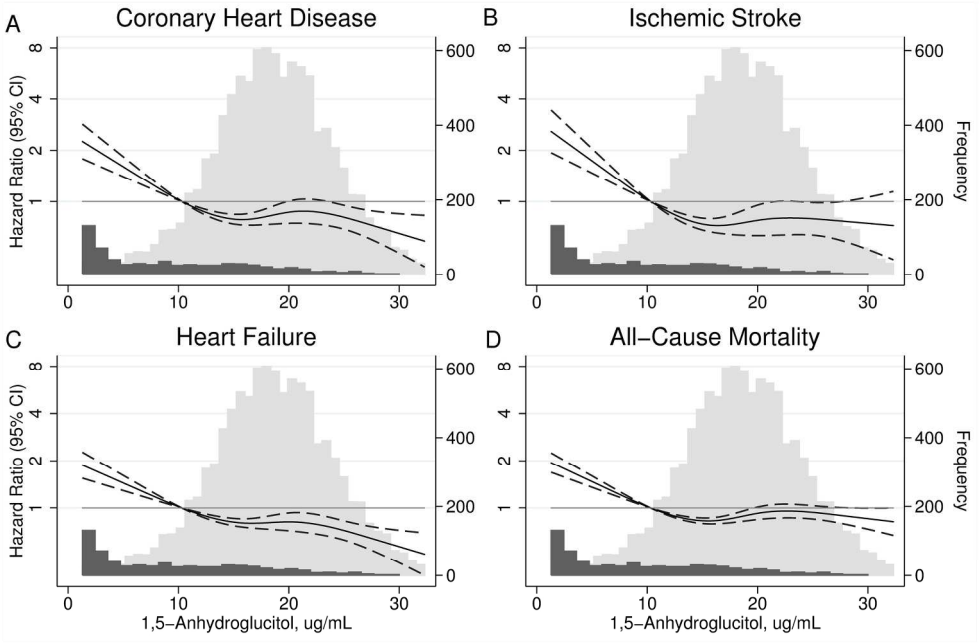

Figure 1
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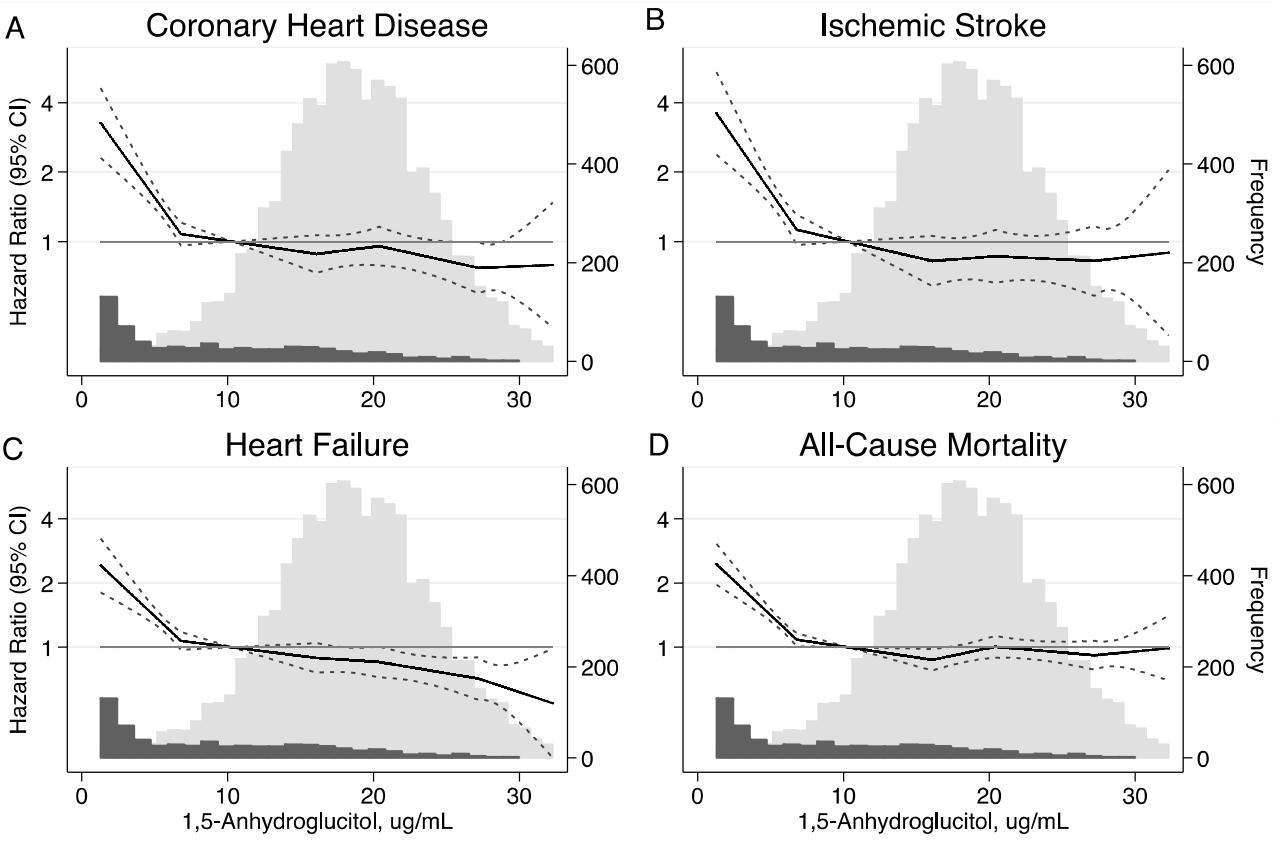
Online Appendix

eFigure 1. Adjusted Hazard Ratios (95% Confidence Intervals) for Baseline 1,5-anhydroglucitol (Modeled Using Linear Splines) with Incident Coronary Heart Disease, Ischemic Stroke, Heart Failure, and Mortality, the ARIC Study, N=11,106



Legend: Adjusted hazard ratios are from Cox proportional hazard regression models. 1,5-anhydroglucitol was modeled using linear splines (solid line) with knots at the 5th, 35th, 65th, and 95th percentiles, and centered at the 10th percentile. 95% confidence intervals are shown with the dashed lines. Models are adjusted for systolic blood pressure (mmHg), blood pressure-lowering medication use (yes, no), education (less than high school, high school or equivalent, more than high school), drinking status (current, former, never), smoking status (current, former, never), physical activity index, glomerular filtration rate (mL/min per 1.73 m², modeled using a linear spline with a knot at the median). Frequency histograms are show for persons without diabetes (light gray bars) and for persons with diabetes (dark gray bars).

eTable 1. Adjusted Hazard Ratios (95% Confidence Intervals) of Baseline Categories of 1,5-Anhydroglucitol (1,5-AG) and Stratified by Diagnosed Diabetes Status with Incident Coronary Heart Disease, Ischemic Stroke, Heart Failure, and Mortality

Outcome	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
Coronary Heart Disease				
N=1159 events (189 in Diabetes)				
No Diagnosis of Diabetes				
1,5-AG ≥ 6 ug/mL	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1,5-AG < 6 ug/mL	1.21 (0.78, 1.86)	1.12 (0.72, 1.72)	0.62 (0.36, 1.05)	0.83 (0.50, 1.39)
Diagnosed Diabetes				
1,5-AG ≥ 6 ug/mL	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1,5-AG < 6 ug/mL	1.41 (1.21, 1.63)	1.45 (1.24, 1.69)	1.21 (0.96, 1.52)	1.25 (1.01, 1.53)
Ischemic Stroke				
N=637 events (99 in Diabetes)				
No Diagnosis of Diabetes				
1,5-AG ≥ 6 ug/mL	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1,5-AG < 6 ug/mL	2.77 (1.90, 4.02)	2.44 (1.67, 3.57)	1.37 (0.83, 2.27)	1.89 (1.17, 3.03)
Diagnosed Diabetes				
1,5-AG ≥ 6 ug/mL	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1,5-AG < 6 ug/mL	1.70 (1.37, 2.12)	1.66 (1.32, 2.08)	1.35 (0.99, 1.84)	1.82 (1.37, 2.41)
Heart Failure				
N=1553 events (262 in Diabetes)				
No Diagnosis of Diabetes				
1,5-AG ≥ 6 ug/mL	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1,5-AG < 6 ug/mL	1.14 (0.80, 1.63)	0.98 (0.68, 1.40)	0.77 (0.51, 1.17)	0.91 (0.60, 1.38)
Diagnosed Diabetes				
1,5-AG ≥ 6 ug/mL	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1,5-AG < 6 ug/mL	1.45 (1.27, 1.64)	1.41 (1.24, 1.61)	1.08 (0.89, 1.31)	1.19 (1.00, 1.41)
All-Cause Mortality				

N=3120 events (392 in Diabetes)				
No Diagnosis of Diabetes				
1,5-AG ≥ 6 ug/mL	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1,5-AG < 6 ug/mL	1.47 (1.18, 1.83)	1.39 (1.12, 1.74)	1.12 (0.87, 1.45)	1.23 (0.95, 1.59)
Diagnosed Diabetes				
1,5-AG ≥ 6 ug/mL	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1,5-AG < 6 ug/mL	1.24 (1.12, 1.37)	1.29 (1.16, 1.43)	1.14 (0.98, 1.33)	1.28 (1.11, 1.46)

Model 1: Age (years), race-center, sex (male, female)
Model 2: Variables in Model 1 + LDL-cholesterol (mg/dL), HDL-cholesterol (mg/dL), triglycerides (mg/dL), body mass index (kg/m^2), waist-to-hip ratio, systolic blood pressure (mmHg), blood pressure-lowering medication use (yes, no), education (less than high school, high school or equivalent, more than high school), drinking status (current, former, never), smoking status (current, former, never), physical activity index, glomerular filtration rate (mL/min per 1.73 m^2, modeled using a linear spline with a knot at the median)
Model 3: Variables in Model 2 + hemoglobin A1c (%)
Model 4: Variables in Model 2 + fasting glucose (mg/dL)
Abbreviations: 1,5-AG, 1,5-anhydroglucitol; CI, confidence interval; HR, hazard ratio.

eTable 2. Adjusted* Hazard Ratios (95% Confidence Intervals) of Baseline Diabetes-Specific Categories of 1,5-Anhydroglucitol (1,5-AG) with Incident Heart Failure and Mortality, Stratified by Median Age at Baseline

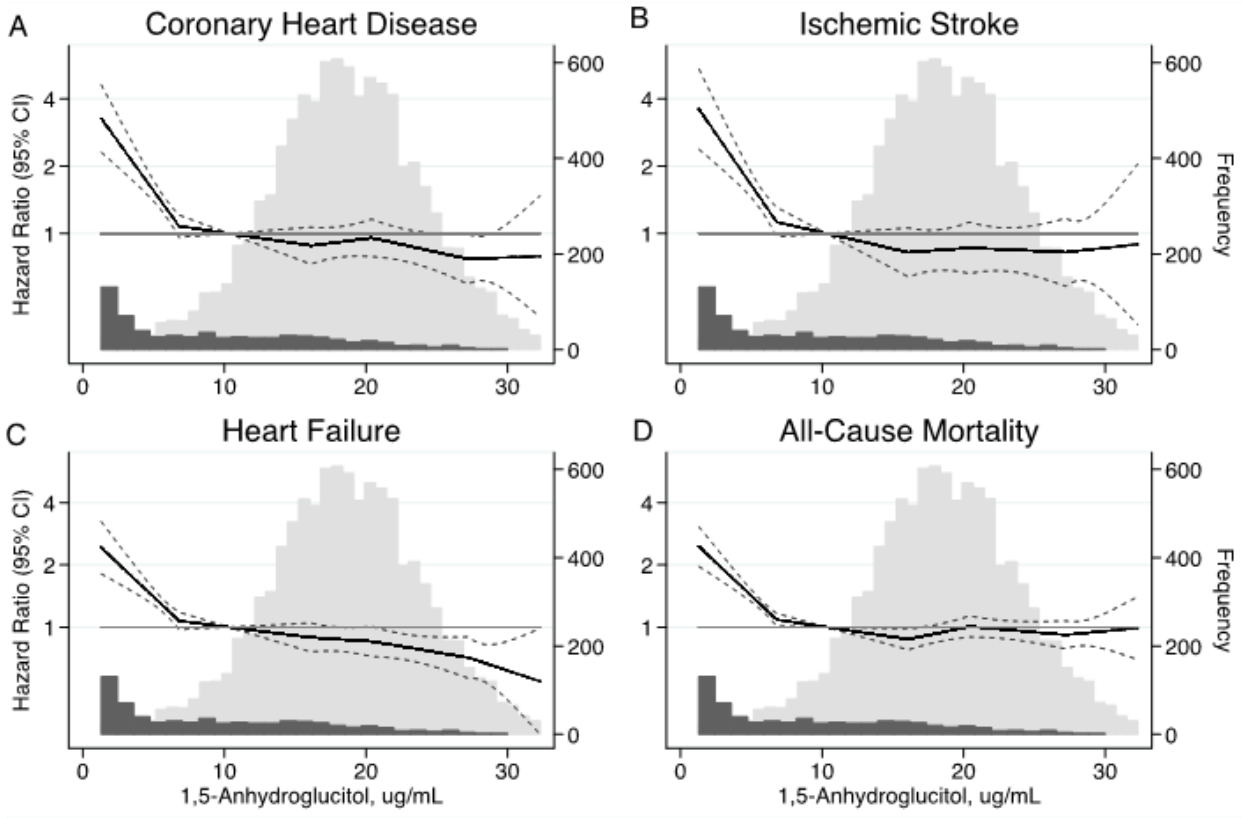
	Heart Failure		Death	
	Age (years)		Age (years)	
	<56.7	≥ 56.7	<56.7	≥ 56.7
No Diagnosis of Diabetes				
1,5-AG ≥ 6 ug/mL	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1,5-AG < 6 ug/mL	1.63 (0.93, 2.84)	0.75 (0.47, 1.20)	1.82 (1.23, 2.70)	1.25 (0.96, 1.64)
Diagnosed Diabetes				
1,5-AG ≥ 6 ug/mL	2.19 (1.50, 3.18)	1.40 (1.10, 1.79)	2.08 (1.58, 2.75)	1.30 (1.08, 1.57)
1,5-AG < 6 ug/mL	5.16 (3.88, 6.87)	2.92 (2.36, 3.62)	2.60 (1.99, 3.40)	2.38 (2.01, 2.83)
p-for-interaction	0.0009		0.0201	

*Adjusted for age (years), race-center, sex (male, female) , LDL-cholesterol (mg/dL), HDL-cholesterol (mg/dL), triglycerides (mg/dL), body mass index (kg/m2), waist-to-hip ratio, systolic blood pressure (mmHg), blood pressure-lowering medication use (yes, no), education (less than high school, high school or equivalent, more than high school), drinking status (current, former, never), smoking status (current, former, never), physical activity index, glomerular filtration rate (mL/min per 1.73 m², modeled using a linear spline with a knot at the median)

Abbreviations: 1,5-AG, 1,5-anhydroglucitol

SUPPLEMENTARY DATA

Supplementary Figure 1. Adjusted Hazard Ratios (95% Confidence Intervals) for Baseline 1,5-anhydroglucitol (Modeled Using Linear Splines) with Incident Coronary Heart Disease, Ischemic Stroke, Heart Failure, and Mortality, the ARIC Study, N=11,106



Legend: Adjusted hazard ratios are from Cox proportional hazard regression models. 1,5-anhydroglucitol was modeled using linear splines (solid line) with knots at the 5th, 35th, 65th, and 95th percentiles, and centered at the 10th percentile. 95% confidence intervals are shown with the dashed lines. Models are adjusted for systolic blood pressure (mmHg), blood pressure-lowering medication use (yes, no), education (less than high school, high school or equivalent, more than high school), drinking status (current, former, never), smoking status (current, former, never), physical activity index, glomerular filtration rate (mL/min per 1.73 m², modeled using a linear spline with a knot at the median). Frequency histograms are show for persons without diabetes (light gray bars) and for persons with diabetes (dark gray bars).

SUPPLEMENTARY DATA

Supplementary Table 1. Adjusted Hazard Ratios (95% Confidence Intervals) of Baseline Categories of 1,5-Anhydroglucitol (1,5-AG) and Stratified by Diagnosed Diabetes Status with Incident Coronary Heart Disease, Ischemic Stroke, Heart Failure, and Mortality

Outcome	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
Coronary Heart Disease				
N=1159 events (189 in Diabetes)				
No Diagnosis of Diabetes				
1,5-AG ≥ 6 ug/mL	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1,5-AG < 6 ug/mL	1.21 (0.78, 1.86)	1.12 (0.72, 1.72)	0.62 (0.36, 1.05)	0.83 (0.50, 1.39)
Diagnosed Diabetes				
1,5-AG ≥ 6 ug/mL	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1,5-AG < 6 ug/mL	1.41 (1.21, 1.63)	1.45 (1.24, 1.69)	1.21 (0.96, 1.52)	1.25 (1.01, 1.53)
Ischemic Stroke				
N=637 events (99 in Diabetes)				
No Diagnosis of Diabetes				
1,5-AG ≥ 6 ug/mL	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1,5-AG < 6 ug/mL	2.77 (1.90, 4.02)	2.44 (1.67, 3.57)	1.37 (0.83, 2.27)	1.89 (1.17, 3.03)
Diagnosed Diabetes				
1,5-AG ≥ 6 ug/mL	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1,5-AG < 6 ug/mL	1.70 (1.37, 2.12)	1.66 (1.32, 2.08)	1.35 (0.99, 1.84)	1.82 (1.37, 2.41)
Heart Failure				
N=1553 events (262 in Diabetes)				
No Diagnosis of Diabetes				
1,5-AG ≥ 6 ug/mL	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1,5-AG < 6 ug/mL	1.14 (0.80, 1.63)	0.98 (0.68, 1.40)	0.77 (0.51, 1.17)	0.91 (0.60, 1.38)
Diagnosed Diabetes				
1,5-AG ≥ 6 ug/mL	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1,5-AG < 6 ug/mL	1.45 (1.27, 1.64)	1.41 (1.24, 1.61)	1.08 (0.89, 1.31)	1.19 (1.00, 1.41)
All-Cause Mortality				
N=3120 events (392 in Diabetes)				
No Diagnosis of Diabetes				
1,5-AG ≥ 6 ug/mL	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1,5-AG < 6 ug/mL	1.47 (1.18, 1.83)	1.39 (1.12, 1.74)	1.12 (0.87, 1.45)	1.23 (0.95, 1.59)
Diagnosed Diabetes				
1,5-AG ≥ 6 ug/mL	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1,5-AG < 6 ug/mL	1.24 (1.12, 1.37)	1.29 (1.16, 1.43)	1.14 (0.98, 1.33)	1.28 (1.11, 1.46)

Model 1: Age (years), race-center, sex (male, female)
Model 2: Variables in Model 1 + LDL-cholesterol (mg/dL), HDL-cholesterol (mg/dL), triglycerides (mg/dL), body mass index (kg/m^2), waist-to-hip ratio, systolic blood pressure (mmHg), blood pressure-lowering medication use (yes, no), education (less than high school, high school or equivalent, more than high school), drinking status (current, former, never), smoking status (current, former, never), physical activity index, glomerular filtration rate (mL/min per 1.73 m², modeled using a linear spline with a knot at the median)
Model 3: Variables in Model 2 + hemoglobin A1c (%)
Model 4: Variables in Model 2 + fasting glucose (mg/dL)
Abbreviations: 1,5-AG, 1,5-anhydroglucitol; CI, confidence interval; HR, hazard ratio.

SUPPLEMENTARY DATA

Supplementary Table 2. Adjusted* Hazard Ratios (95% Confidence Intervals) of Baseline Diabetes-Specific Categories of 1,5-Anhydroglucitol (1,5-AG) with Incident Heart Failure and Mortality, Stratified by Median Age at Baseline

	Heart Failure		Death	
	Age (years)		Age (years)	
	<56.7	≥ 56.7	<56.7	≥ 56.7
No Diagnosis of Diabetes				
1,5-AG ≥ 6 ug/mL	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1,5-AG < 6 ug/mL	1.63 (0.93, 2.84)	0.75 (0.47, 1.20)	1.82 (1.23, 2.70)	1.25 (0.96, 1.64)
Diagnosed Diabetes				
1,5-AG ≥ 6 ug/mL	2.19 (1.50, 3.18)	1.40 (1.10, 1.79)	2.08 (1.58, 2.75)	1.30 (1.08, 1.57)
1,5-AG < 6 ug/mL	5.16 (3.88, 6.87)	2.92 (2.36, 3.62)	2.60 (1.99, 3.40)	2.38 (2.01, 2.83)
p-for-interaction	0.0009		0.0201	

*Adjusted for age (years), race-center, sex (male, female) , LDL-cholesterol (mg/dL), HDL-cholesterol (mg/dL), triglycerides (mg/dL), body mass index (kg/m2), waist-to-hip ratio, systolic blood pressure (mmHg), blood pressure-lowering medication use (yes, no), education (less than high school, high school or equivalent, more than high school), drinking status (current, former, never), smoking status (current, former, never), physical activity index, glomerular filtration rate (mL/min per 1.73 m^2, modeled using a linear spline with a knot at the median)

Abbreviations: 1,5-AG, 1,5-anhydroglucitol