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Establishment of Community-Based Reference Intervals for Fructosamine, Glycated Albumin, and 1,5-Anhydroglucitol

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BACKGROUND: There is growing interest in fructosamine, glycated albumin, and 1,5-anhydroglucitol (1,5-AG) as alternative measures of hyperglycemia, particularly for use in settings where traditional measures (glucose and HbA1c) are problematic or where intermediate (2–4 weeks) glycemic control is of interest. However, reference intervals for these alternative biomarkers are not established.

METHODS: We measured fructosamine, glycated albumin, and 1,5-AG in a community-based sample of US black and white adults who participated in the Atherosclerosis Risk in Communities (ARIC) Study. We calculated reference intervals, evaluated demographic differences, and derived cutoffs aligned with current diagnostic cutpoints for HbA1c and fasting glucose.

RESULTS: In a healthy reference population of 1799 individuals (mean age, 55 years; 51% women; 15% black), the 2.5 and 97.5 percentiles, respectively, were 194.8 and 258.0 μmol/L for fructosamine, 10.7% and 15.1% for glycated albumin, and 8.4 and 28.7 μg/mL for 1,5-AG. Distributions differed by race, sex, and body mass index. Equivalent concentrations of fructosamine and glycated albumin corresponding to an HbA1c of 6.5% (96.5 percentile) were 270.2 μmol/L and 15.6%, respectively. Equivalent concentrations of fructosamine and glycated albumin corresponding to a fasting glucose of 126 mg/dL (93.9 percentile) were 261.7 μmol/L and 15.0%, respectively.

CONCLUSIONS: The reference intervals for these biomarkers should inform their clinical use. Diagnostic cutpoint equivalents for fructosamine and glycated albumin could be useful to identify persons with hyperglycemia in settings where fasting glucose or HbA1c are not available or where the interpretation of these traditional measures is problematic.

There is growing interest in nontraditional biomarkers of hyperglycemia, particularly for use in settings where intermediate (2–4 weeks) glycemic control is of interest or where traditional measures (glucose and HbA1c) are problematic. For example, HbA1c may be influenced by alterations in erythrocyte lifespan or hemoglobin, independent of glycemia *(1)*. Three molecules of particular interest are fructosamine, glycated albumin, and 1,5-anhydroglucitol (1,5-AG). These markers of chronic hyperglycemia are extracellular and therefore independent of changes in erythrocytes or hemoglobin.

Fructosamine reflects the binding of glucose to all serum proteins, predominately albumin but also other proteins including globulins and lipoproteins. Glycated albumin is a measure of glucose bound specifically to serum albumin and is commonly expressed as a percentage of total serum albumin. Due to the rate of turnover of serum proteins, fructosamine and glycated albumin concentrations correspond to approximately 2–4 weeks of past exposure to blood glucose. 1,5-AG is a monosaccharide that is normally stable in serum; it is ubiquitous in the diet. 1,5-AG closely resembles glucose in structure (it is the 1-deoxy form of glucose) and, like glucose, it is freely filtered by the glomeruli and normally reabsorbed in the renal proximal tubule. However, when glucose concentrations in the blood exceed the renal threshold (overt hyperglycemia, occurring at glucose concentrations of approximately 160–180 mg/dL), glucose will compete with 1,5-AG for reabsorption in the tubule, leading to urinary excretion of 1,5-AG and causing serum concentrations to drop. Thus, low serum 1,5-AG is

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thought to be a useful biomarker of hyperglycemic excursions occurring over the previous 1–2 weeks *(2)*.

Reliable reference intervals are central to medical decision-making. A barrier to the routine clinical use of fructosamine, glycated albumin, and 1,5-AG is the lack of agreed-upon reference intervals or "normal" values for these biomarkers. Previous studies examining the reference intervals and potential clinical cutpoints for fructosamine or glycated albumin have been small ($n < 200$) and the study populations have typically not been well characterized *(3, 4)*. Furthermore, the literature on glycated albumin has largely focused on persons in Japan, Korea, and other Asian populations, where the assay is in wide clinical use *(5–10)*.

The objective of this study was to define the reference intervals and demographic differences in fructosamine, glycated albumin, and 1,5-AG by use of data from a well-characterized community-based US population of black and white adults. We also derived "HbA1c-equivalent" diabetes diagnostic cutpoints for fructosamine and glycated albumin. The knowledge of clinically relevant cutpoints for fructosamine or glycated albumin could be useful in settings where HbA1c is not available or in those conditions where its interpretation is problematic.

Methods

STUDY POPULATION

We conducted this study using data from the community-based Atherosclerosis Risk in Communities (ARIC) Study, a large cohort of over 15 000 mostly black and white middle-aged adults from 4 US communities: suburban Minneapolis; Forsyth County, North Carolina; Washington County, Maryland; and Jackson, Mississippi. Fructosamine, glycated albumin, and 1,5-AG data were available for participants who attended the second clinical examination, ARIC Visit 2, which took place from 1990–1992. To establish the reference intervals, we followed the approach established by the Clinical and Laboratory Standards Institute *(11)*. To derive a "healthy" reference population, we included here participants without diagnosed diabetes. Using the Tukey approach *(11)*, we excluded outliers and sequentially excluded ARIC participants who were nonfasting, were missing variables of interest, had serum album <3 g/dL, had increased liver enzymes, were current smokers, had clinical or subclinical thyroid dysfunction, had reduced kidney function, had prevalent coronary heart disease, had hypertension, or had dyslipidemia. Our main analyses included a "healthy" reference population of 1799 participants (see Fig. 1 in the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol64/issue5). To derive cutpoints for fructosamine and glycated albumin that were equivalent to diagnostic cutpoints for HbA1c and fasting glucose, we used the larger ARIC Study population of 11 737 participants without a history of diagnosed diabetes (see Fig. 1 in the online Data Supplement).

Study protocols were approved by institutional review boards at each study site, and informed consent was obtained from all participants.

LABORATORY MEASUREMENTS

Measurements of fructosamine, glycated albumin, and 1,5-AG were conducted in 2012–2013 in stored serum samples originally collected from participants at Visit 2 (1990–1992) and stored at −70 °C. These 3 assays were analyzed on the Roche Modular P800 analyzer at the University of Minnesota.

Fructosamine was quantified by use of a colorimetric assay (Roche Diagnostics Corp.). The CVs were 3.2% at a concentration of 212.6 μmol/L and 2.5% at a concentration of 856.7 μmol/L.

Glycated albumin was measured using an assay that requires separate measurements of total albumin (bromocresol purple) and glycated albumin (enzymatic method utilizing ketoamine oxidase and an albumin-specific protease) (Lucica GA-L Glycated Albumin, Asahi Kasei Pharma Corp.). The glycated albumin result was expressed as a percentage of total albumin according to the manufacturer's formula: [(glycated albumin concentration in g/dL/serum albumin concentration in g/dL) × 100/1.14] + 2.9. The CVs for glycated albumin were 1.8% at a mean value of 56.0% and 2.1% at a mean value of 22.7%.

1,5-AG was measured by use of the GlycoMark assay (GlycoMark, Inc.). The CVs were 3.8% at a mean concentration of 4.6 μg/mL and 1.3% at a mean concentration of 14.7 μg/mL.

We compared the fructosamine, glycated albumin, and 1,5-AG results to fasting glucose and HbA1c measurements also available from participants at ARIC Visit 2. Serum glucose was measured as part of the original ARIC Study protocol by the hexokinase method *(12)*. HbA1c was measured in EDTA whole blood by use of Tosoh instruments (Tosoh A1C 2.2 Plus Glycohemoglobin Analyzer in 2003–2004 and the Tosoh G7 method in 2007–2008, Tosoh Corp.) *(13)*. Both Tosoh instruments are NGSP-certified, standardized to the Diabetes Control and Complications Trial assay, and performed in an NGSP Secondary Laboratory (University of Minnesota).

STATISTICAL ANALYSES

We examined the distributions and summary statistics including the mean, SD, minimum, maximum, median, and percentiles (p2.5, p25, p50, p75, p95, p97.5) of fructosamine, glycated albumin, and 1,5-AG in our reference population. To evaluate the impact of the exclu-

Table 1. Characteristics of referent population, healthy subsample of the Atherosclerosis Risk in Communities (ARIC) Study, *n* = 1799.

Variable	Mean (SD) or %
Age, years	55.3 (5.4)
Female, %	51.4
Black, %	14.5
Categories of body mass index	
<25 kg/m^2	40.1
25 to <30 kg/m^2	40.7
≥30 kg/m^2	19.1
LDL cholesterol, mg/dL	104.6 (20.9)
HDL cholesterol, mg/dL	15.0 (9.0)
Triglycerides, mg/dL	106.2 (53.1)
Systolic blood pressure, mmHg	113.2 (12.1)
Diastolic blood pressure, mmHg	69.8 (8.0)
eGFR, mL/min/1.73 m^2	97.6 (12.4)

sions, we examined the change in the distribution after each exclusion. We derived reference intervals by use of a nonparametric approach based on the 2.5th and 97.5 percentiles and corresponding 90% confidence intervals in the reference population *(14)*.

Using forest plots and histograms, we visually displayed and compared the distributions across subgroups. For only fructosamine and glycated albumin (as 1,5-AG is not proposed as a diagnostic test), we evaluated percentiles of each biomarker corresponding to diabetes diagnostic cutpoints for HbA1c (5.7% and 6.5%) and fasting glucose (100 and 126 mg/dL) *(15)*. We calculated the Pearson correlations between biomarkers and generated scatterplots with corresponding regression and LOWESS curves. We also specifically examined associations of the different biomarkers with body mass index. Because there is current debate regarding whether fructosamine should be corrected for total serum protein concentration, we compared the Pearson correlations of fructosamine with HbA1c and glycated albumin both before and after correction for serum albumin with published equations *(*16–19*)*.

Results

Characteristics of the referent population of 1799 middle-aged adults are shown in Table 1. The means (SDs) for fructosamine, glycated albumin, and 1,5-AG were 225.8 (16.4) μmol/L, 12.7% (1.1%), and 18.4 (5.1) μg/mL, respectively (Table 2). By way of comparison, the means (SDs) for HbA1c and fasting glucose in this same reference population were 5.3% (0.3%) and 100.3 (9.3) mg/dL, respectively. The exclusion of diagnosed diabetes made a substantial impact on the distributions of the biomarkers, while the other exclusions had relatively small effects (see Fig. 2 in the online Data Supplement). After exclusions, the reference intervals (2.5 and 97.5 percentiles) in the overall reference population were 194.8 and 258.0 μmol/L for fructosamine; 10.7% and 15.1% for glycated albumin; and 8.4 and 28.7 μg/mL for 1,5-AG (Table 2).

Concentrations of fructosamine were slightly higher in men than women, lower in whites than blacks, higher at older ages, and lower at higher categories of body mass index (Table 2; see Fig. 3, panel A in the online Data Supplement). Patterns of demographic differences were similar for glycated albumin, except for sex when females had higher values than males (Table 2; see Fig. 3, panel B in the online Data Supplement). We observed inverse associations of fructosamine and glycated albumin with body mass index; this was in contrast to the positive associations of fasting glucose and HbA1c with body mass index (see Fig. 4 in the online Data Supplement).

1,5-AG concentrations were lower in women than men, lower in whites than blacks, and lower at higher ages but not significantly so (Table 2; see Fig. 3, Panel C in the online Data Supplement). 1,5-AG was higher at higher categories of body mass index.

The distributions of HbA1c and fasting glucose are shown in Table 1 in the online Data Supplement. The concentrations of fructosamine corresponding to prediabetes and diabetes clinical cutpoints of 5.7% and 6.5% for HbA1c, based on percentiles, were 241.4 μmol/L (the 77.1 percentile) and 270.2 μmol/L (the 96.5 percentile), respectively (Table 3). The corresponding values of glycated albumin were 13.6% and 15.6%, respectively. The concentrations of fructosamine corresponding to prediabetes and diabetes clinical cutpoints of 100 and 126 mg/dL for fasting glucose were 224.9 μmol/L (the 45.3 percentile) and 261.7 μmol/L (the 93.9 percentile), respectively. The corresponding values for glycated albumin were 12.5% and 15.0%, respectively.

After fructosamine was corrected for serum albumin by use of published equations, correlations of fructosamine with HbA1c and with glycated albumin were strengthened (see Table 2 in the online Data Supplement). Scatterplots and correlations of the different biomarkers are shown in Fig. 5 in the online Data Supplement.

Discussion

The present study established reference intervals for 3 nontraditional assays of chronic hyperglycemia. The Roche fructosamine assay has been approved for clinical use for many years and is the dominant glycated protein assay used in the US. The Asahi Kasei Lucica GA-L gly-

Table 2. Nonparametric reference intervals of fructosamine, glycated albumin, and 1,5-anhydroglucitol, overall and according to sex, race, age, and body mass index, $n = 1799$.

	n	Mean (SD)	2.5 percentile (90% CI)	25th percentile	Median	75th percentile	97.5 percentile (90% CI)
Fructosamine, μmol/L							
Overall	1799	225.8 (16.4)	194.8 (192.1, 196.2)	214.3	225.6	236.3	258.0 (256.4, 260.4)
Overall excluding BMI ≥30 kg/m^2	1455	227.4 (16.1)	197.4 (195.4, 198.9)	216.5	226.9	238.0	259.2 (257.2, 264.0)
Sex							
Male	875	226.1 (15.9)	193.7 (190.0, 196.6)	216.0	226.4	236.6	256.5 (255.2, 258.0)
Female	924	225.4 (16.9)	195.4 (192.0, 196.7)	213.4	224.9	235.8	263.3 (257.3, 267.7)
P value[a]		0.186			0.371		
Race							
Black	261	231.8 (18.3)	198.2 (195.4, 199.6)	219.0	232.6	245.8	267.8 (263.8, 273.1)
White	1538	224.8 (15.8)	193.8 (191.8, 195.1)	214.1	224.5	234.9	256.0 (254.5, 258.4)
P value[a]		<0.001			<0.001		
Age (tertiles)							
47–52 years	707	224.3 (16.2)	191.9 (189.4, 195.9)	213.2	224.8	235.1	254.5 (253.1, 258.0)
53–57 years	499	226.7 (16.9)	194.8 (192.0, 197.4)	215.2	225.7	237.7	265.1 (258.0, 268.2)
58–68 years	593	226.7 (16.1)	196.5 (193.8, 198.3)	215.2	226.2	237.7	258.7 (255.8, 263.4)
P value[a]		0.437			0.009		
Categories of body mass index							
<25 kg/m^2	722	230.5 (16.1)	200.0 (196.7, 202.5)	220.3	230.3	241.2	263.6 (259.4, 266.8)
25 to <30 kg/m^2	733	224.3 (15.4)	196.5 (193.8, 198.3)	213.4	223.9	234.1	254.5 (252.1, 258.5)
≥30 kg/m^2	344	218.9 (16.1)	188.3 (183.4, 190.8)	208.1	217.8	229.3	251.7 (247.6, 256.1)
P value[a]		<0.001			<0.001		
Glycated albumin, %							
Overall	1799	12.7 (1.1)	10.7 (10.5, 10.8)	11.9	12.7	13.5	15.1 (15.0, 15.3)
Overall excluding BMI ≥30 kg/m^2	1455	12.9 (1.1)	10.9 (10.8, 10.9)	12.1	12.8	13.6	15.2 (15.1, 15.4)
Sex							
Male	875	12.6 (1.1)	10.5 (10.3, 10.8)	11.8	12.6	13.3	15.0 (14.7, 15.1)
Female	924	12.9 (1.2)	10.8 (10.6, 10.9)	12.1	12.9	13.7	15.3 (15.1, 15.5)
P value[a]		<0.001			<0.001		
Race							
Black	261	13.3 (1.2)	10.9 (10.4, 11.3)	12.6	13.3	14.2	15.5 (15.3, 15.6)
White	1538	12.7 (1.1)	10.7 (10.5, 10.8)	11.9	12.6	13.4	14.9 (14.7, 15.1)
P value[a]		<0.001			<0.001		
Age (tertiles, years)							
47–52	707	12.7 (1.1)	10.8 (10.5, 10.8)	11.9	12.6	13.4	14.9 (14.7, 15.4)
53–57	499	12.8 (1.1)	10.6 (10.4, 10.9)	12.0	12.7	13.4	15.1 (15.0, 15.3)
58–68	593	12.8 (1.2)	10.7 (10.4, 10.9)	12.0	12.8	13.6	15.3 (15.1, 15.5)
P value[a]		0.087			0.079		

Continued on page XX

Table 2. Nonparametric reference intervals of fructosamine, glycated albumin, and 1,5-anhydroglucitol, overall and according to sex, race, age, and body mass index, *n* = 1799. *(Continued from page XX)*

	n	Mean (SD)	2.5 percentile (90% CI)	25th percentile	Median	75th percentile	97.5 percentile (90% CI)
Categories of body mass index							
<25 kg/m^2	722	13.1 (1.1)	11.0 (10.9, 11.1)	12.3	13.1	13.8	15.3 (15.2, 15.6)
25 to <30 kg/m^2	733	12.6 (1.1)	10.8 (10.5, 10.9)	11.9	12.6	13.3	15.0 (14.7, 15.2)
≥30 kg/m^2	344	12.3 (1.1)	10.2 (10.1, 10.3)	11.5	12.3	13.0	14.4 (14.4, 14.8)
P value[a]		<0.001			<0.001		
1,5-anhydroglucitol, ug/mL							
Overall	1799	18.4 (5.1)	8.4 (7.8, 8.8)	15.0	18.3	21.8	28.7 (28.3, 29.1)
Overall excluding BMI ≥30 kg/m^2	1455	18.3 (5.0)	8.5 (8.1, 9.2)	14.9	18.1	21.6	28.7 (28.3, 29.2)
Sex							
Male	875	19.6 (5.2)	8.5 (7.4, 9.5)	16.1	19.8	23.4	29.2 (28.7, 30.3)
Female	924	17.3 (4.7)	8.2 (7.7, 8.8)	14.3	17.2	20.3	27.3 (26.5, 28.3)
P value[a]		<0.001			<0.001		
Race							
Black	261	16.9 (4.7)	7.7 (7.2, 8.6)	14.0	16.4	20.0	27.2 (25.4, 28.7)
White	1538	18.7 (5.1)	8.5 (7.9, 9.1)	15.2	18.6	22.1	28.8 (28.5, 29.5)
P value[a]		<0.001			<0.001		
Age (tertiles, years)							
47–52	707	18.2 (5.1)	8.3 (7.5, 8.8)	14.7	18.1	21.6	28.6 (27.9, 30.2)
53–57	499	18.7 (5.0)	8.8 (7.5, 10.0)	15.3	18.5	22.0	28.7 (27.6, 29.5)
58–68	593	18.5 (5.1)	8.0 (7.4, 9.2)	15.2	18.3	21.7	28.7 (28.1, 29.5)
P value[a]		0.485			0.305		
Categories of body mass index							
<25 kg/m^2	722	18.1 (5.0)	8.9 (7.7, 9.7)	14.6	17.7	21.4	28.7 (28.1, 29.9)
25 to <30 kg/m^2	733	18.5 (5.0)	8.5 (7.9, 8.9)	15.3	18.3	22.0	28.6 (27.8, 29.2)
≥30 kg/m^2	344	18.9 (5.2)	7.5 (6.4, 8.4)	15.6	19.3	22.3	28.9 (27.5, 30.2)
P value[a]		<0.001			0.066		

[a] *P* value for difference in medians from nonparametric equality-of-medians test or difference in means from *t*-test (2 groups) or ANOVA (3 groups).

cated albumin assay is used widely in Japan and other countries in Asia and was FDA-cleared for clinical use in the US in October 2017. The GlycoMark 1,5-AG assay is approved for clinical use in the US and is reimbursed by Medicare and some other insurers, but is not widely used. Our results provide standard values that are likely to facilitate clinical interpretation of each of these assays.

The reference interval for fructosamine reported in the Roche package insert is 205–285 μmol/L. This range was derived from data published in 1989 from 555 "apparently healthy" blood donors between 20 and 60 years of age *(20)*. Our reference interval of 195–258 μmol/L suggests that the reference interval for this assay may need to be updated based on modern clinical performance data.

The distribution of glycated albumin in our study population was similar to a study of 1334 Italian blood donors, which showed similar patterns for sex and age and a 97.5 percentile of 14.5% with use of an enzymatic assay *(21)*. A previous study in 201 healthy US study participants without known diabetes and with normal glucose tolerance identified a reference interval of 11.9%–15.8% for glycated albumin *(4)*. Higher values in blacks than whites and women than men were also observed, although the sex difference was not statistically significant, possibly owing to the limited power in this

Table 3. Percentile equivalents for fructosamine, glycated albumin, and 1,5-anhydroglucitol, based on clinical cutpoints for HbA1c and fasting glucose in the total population of persons without diagnosed diabetes, *n* = 11 737.

	HbA1c		Fasting glucose	
	5.7%	6.5%	100 mg/dL	126 mg/dL
Percentile:	77.1	96.5	45.3	93.9
Fructosamine, μmol/L	241.4	270.2	224.9	261.7
Glycated albumin, %	13.6	15.6	12.5	15.0
1,5-anhydroglucitol, μg/mL	29.1	22.7	27.5	17.9

small study. The prediabetes diagnostic threshold for glycated albumin determined in the present study (13.6%) is similar to that in a previous study of a cohort of 236 African immigrants that used the same glycated albumin assay and identified a threshold of 13.8% (the percentile equivalent of an HbA1c of 5.7% in their study population) *(22)*.

Lower values of both fructosamine and glycated albumin at higher categories of body mass index have been previously reported *(22–25)*, with U- or J-shaped associations of fructosamine and glycated albumin with body mass index. This is in contrast to the associations of fasting glucose and HbA1c with body mass index, which tends to be positive and roughly linear. The reasons for lower concentrations of fructosamine and glycated albumin at high levels of adiposity remains unexplained but may relate to high levels of inflammation or issues related to protein turnover *(26, 27)*.

The diabetes diagnostic cutpoint of 6.5% for HbA1c was chosen for its specificity *(28)*. Indeed, in our reference population, an HbA1c of 6.5% corresponded to the 96.5 percentile, whereas the diagnostic fasting glucose cutpoint of 126 mg/dL corresponded to the 93.9 percentile. Thus, the "equivalent" fructosamine and glycated albumin values were higher for HbA1c than fasting glucose. The "diagnostic" cutpoint equivalents for fructosamine and glycated albumin provided in the present study may be useful in studies that do not have fasting blood samples for the measurement of glucose or whole blood samples for the measurement of HbA1c. Indeed, many cohorts have stored nonfasting plasma or serum in which fructosamine or glycated albumin could be reliably measured and used to determine the glycemic status of the study population.

Diagnostic cutpoints are distinct from reference intervals and are typically derived based on a synthesis of multiple types of evidence, including, but not limited to, diagnostic testing studies, randomized clinical trials, epidemiologic evidence, and cost-effectiveness analyses. Recommendations for specific diagnostic cutpoints are often highly political and controversial. Our goal here was not to debate the optimal diagnostic or screening cutpoints for fructosamine or glycated albumin, but to equate these biomarkers to existing clinically relevant cutpoints for HbA1c. The biology of fructosamine and glycated albumin are similar to HbA1c, and correlations between these biomarkers are high in the setting of hyperglycemia *(29, 30)*.

The 1,5-AG assay reflects hyperglycemia only when glucose exceeds the renal threshold. By design, our study population was limited to a "healthy" reference group. Thus, no participants in the present study had concentrations of blood glucose exceeding the renal threshold (maximum fasting glucose was 130 mg/dL in our study). 1,5-AG concentrations <10 μg/mL are believed to reflect "frequent" hyperglycemic excursions above the renal threshold *(2)*. However, in our study population, there were 88 individuals (4.9%) with 1,5-AG concentrations <10 μg/mL. The demographic differences observed for 1,5-AG in the present study may reflect nonglycemic factors such as dietary differences or other determinants of 1,5-AG in persons without diabetes *(31)*. Indeed, our recent genetic analyses suggest that 1,5-AG concentrations may also reflect the speed of glucose digestion and enteric uptake in persons without diabetes *(32)*.

Some limitations of this study that should be considered in the interpretation of our results include that our study population was limited to middle-aged black and white adults (age range, 47–68 years; 15% black). Nonetheless, this population is likely largely generalizable to the majority of the US population to whom these tests might be applied. For specific patient populations, such as pregnant women, additional studies are warranted. We did not have serum albumin concentrations as measured with the bromocresol green assay method in this study. Corrections for fructosamine in the present study were conducted by use of the Asahi Kasei serum albumin (bromocresol purple). The assays examined in the present study are not formally standardized in the US, which suggests that these results may not apply to other methods implemented at other laboratories. Nonetheless, because the Roche fructosamine assay is the predominant serum glycated protein assay in the US, our results for this assay may be fairly generalizable. Indeed, 95% of participants in the 2016 College of American Patholo-

gists fructosamine survey used the Roche method, and results are similar among laboratories (CV < 3.5%), suggesting that standardization is not a substantial issue for this method in the US *(33)*. An additional limitation is that all measurements were conducted in long-term stored samples. Nonetheless, we demonstrated excellent analytical performance of these assays (CVs < 4%), and prior studies have demonstrated high reliability of these assays in stored samples *(34–38)*.

In conclusion, we defined a healthy population within the community-based ARIC cohort to establish reference intervals for fructosamine, glycated albumin, and 1,5-AG, overall and in important demographic subgroups. We also identified fructosamine and glycated albumin cutpoints corresponding to values of HbA1c and fasting glucose used for diagnosis and screening of diabetes. The results of this study should help inform the clinical use of the Roche fructosamine, Asahi Kasei glycated albumin, and GlycoMark 1,5-AG assays.

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