Nontraditional Markers of Glycemia

Associations with microvascular conditions

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OBJECTIVE—To compare the associations of nontraditional (fructosamine, glycated albumin, 1,5-anhydroglucitol [1,5-AG]) and standard (fasting glucose, HbA_{1c}) glycemic markers with common microvascular conditions associated with diabetes mellitus.

RESEARCH DESIGN AND METHODS—We conducted a cross-sectional study of 1,600 participants (227 with a history of diabetes and 1,323 without) from the Atherosclerosis Risk in Communities (ARIC) Study, a community-based population. We conducted logistic regression analyses of the associations of diabetes-specific tertiles of fructosamine, glycated albumin, 1/(1,5-AG), fasting glucose, and HbA_{1c} with prevalence of chronic kidney disease, albuminuria, and retinopathy after adjustment for demographic, clinical, and lifestyle variables.

RESULTS—We observed significant positive trends in the associations of each marker with albuminuria and retinopathy, even after accounting for demographic, clinical, and lifestyle factors (all P trends <0.05). The associations with chronic kidney disease were similar in direction but were only significant for higher glycated albumin (P trend = 0.005), fructosamine (P trend = 0.003), and HbA_{1c} (P trend = 0.005) values. After further adjustment for HbA_{1c}, glycated albumin and fructosamine remained significantly or borderline significantly associated with the microvascular outcomes.

CONCLUSIONS—In cross-sectional analyses, two serum markers of glycemia—glycated albumin and fructosamine—are as, or more strongly, associated with microvascular conditions as HbA_{1c}. These markers may be useful in settings where whole blood is not available. Whether they might complement or outperform HbA_{1c} in terms of long-term predictive value requires further investigation.

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HbA_{1c} is the gold-standard measure for assessment of glycemic control and has recently been recommended for use in the diagnosis of diabetes (1). HbA_{1c} results from the glycation of hemoglobin in erythrocytes and represents long-term (2–3 months) glycemia. Nonetheless, HbA_{1c} has important limitations (1), and it is possible that nontraditional serum markers of glycemia, such as fructosamine, glycated albumin, and 1,5-anhydroglucitol (1,5-AG), may have added clinical utility. Glycated albumin and fructosamine reflect the modification of serum proteins by glucose and are markers of endogenous glucose exposure over the prior 2 to 4 weeks, i.e., extending beyond the half-life of albumin and some other serum proteins. 1,5-AG is a marker of glycemia-induced glycosuria, since reabsorption of filtered 1,5-AG in the proximal tubule is competitively inhibited by glucose (2,3). Lower serum 1,5-AG reflects high circulating glucose and the occurrence of glycosuria over the previous 1 to 2 weeks (3,4). These serum markers may be useful as adjuncts to HbA_{1c} to provide information on short-term (e.g., 2–4 weeks) glycemic control and glycemic excursions, and/or for monitoring glycemic control when interpretation of HbA_{1c} is problematic (e.g., in the presence of hemoglobinopathies, iron deficiency, and other anemias). However, few studies have examined the association of serum glycemic markers with complications (5). The objective of this study was to characterize and compare the associations of nontraditional (fructosamine, glycated albumin, 1,5-AG) and standard (fasting glucose, HbA_{1c}) glycemic markers with common microvascular conditions associated with diabetes in a general population.

RESEARCH DESIGN AND METHODS

Study population

We conducted a cross-sectional study of participants from the Atherosclerosis Risk in Communities (ARIC) Study who participated in the ARIC Carotid MRI (CARMRI) substudy. The ARIC Study is an ongoing prospective cohort study of 15,792 black and white adults originally enrolled between 1987 and 1989 (6). Just over 2,000 participants from the original cohort, now aged 60–84 years, were recruited into the CARMRI substudy in 2004 and 2005 using a stratified sampling plan (7). In addition to the MRI examination, trained technicians performed a comprehensive clinical examination, obtained blood specimens, and conducted an interview to obtain information on health status and risk factors. Our study sample was limited to 1,600 participants (227 with a history of diabetes and 1,323 without) after excluding those who fasted less than 8 h (N = 20) or who were missing variables of interest (N = 402). An additional 51 participants had missing or ungradable retinal photographs and were further excluded from our analyses of retinopathy.

Institutional review boards at each clinical site approved the study protocol, and written informed consent was obtained from all participants.

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Glycemic markers

HbA_{1c} was measured from whole-blood samples as part of the original CARMRI protocol using the Tina-quant II method (Roche Diagnostics, Basel, Switzerland) implemented on a Roche Hitachi 911 Analyzer. This method is aligned to the Diabetes Control and Complications Trial assay. In 2009, we measured glycated albumin (Asahi Kasei Lucica GA-L; Asahi Kasei Pharma Corporation, Tokyo, Japan)—expressed as a percentage of total serum albumin, fructosamine (Roche Diagnostics), and 1,5-AG (GlycoMark, Winston-Salem, NC) from stored serum specimens using a Roche Modular P800 system. The interassay coefficients of variation (CVs) were 2.7% for glycated albumin, 3.7% for fructosamine, and 4.8% for 1,5-AG.

Outcomes

We focused on three microvascular conditions: chronic kidney disease, albuminuria, and retinopathy. Serum creatinine was measured using a Roche enzymatic assay, calibrated by the manufacturer to be traceable to reference method procedures (standard creatinine). The glomerular filtration rate (GFR) was estimated using the four-variable Modification of Diet in Renal Disease (MDRD) Study formula re-expressed to use standard creatinine and reported in milliliters per minute per 1.73 m^2 (8–10). People with estimated GFR (eGFR) below 60 mL/min/1.73 m^2 were considered to have chronic kidney disease (11). Urine albumin and creatinine were measured from random spot urine collected at the CARMRI visit using a clean-catch technique and sterile containers. We defined albuminuria as a urine albumin-to-creatinine ratio of 30 mg/g or higher and conducted sensitivity analyses excluding those people with macroalbuminuria (albumin-to-creatinine ratio ≥300 mg/g). Retinal photographs were taken following a standardized protocol that has been previously documented (12). Briefly, after 5 min of dark adaptation, a nonmydriatic 45-degree retinal photograph centered on the optic disc and macula was taken of one randomly selected eye. Trained readers masked to participant information evaluated each of the photographs. We defined retinopathy (moderate to severe) as a severity score greater than or equal to 35 according to a modification of the Airlie House classification system, as used in the Early Treatment Diabetic Retinopathy Study (ETDRS) (12,13).

Table 1—*Participant characteristics overall and by diabetes history*

	All	Diabetes	No diabetes
N	1,600	277	1,323
Age (years)	70.4 (0.2)	70.3 (0.4)	70.4 (0.2)
Men (%)	43.1 (1.5)	48.2 (3.9)	42.1 (1.7)
Black (%)	18.7 (0.3)	32.0 (1.4)	16.3 (0.3)
Education (%)			
Less than high school	15.0 (1.0)	19.0 (2.6)	14.3 (1.1)
High school or equivalent	44.9 (1.6)	49.0 (3.8)	44.2 (1.7)
College or above	40.1 (1.5)	32.0 (3.6)	41.5 (1.7)
Family history of diabetes (%)	23.5 (1.3)	37.4 (3.7)	21.0 (1.4)
Previous history of coronary heart disease (%)	9.7 (0.8)	16.4 (2.6)	8.4 (0.9)
Blood pressure medication use (%)	64.7 (1.5)	85.4 (3.0)	60.9 (1.7)
Cholesterol-lowering medication use (%)	44.9 (1.5)	70.4 (3.5)	40.3 (1.7)
Smoking status (%)			
Current	7.9 (0.8)	7.6 (2.1)	7.9 (0.9)
Former	41.4 (1.5)	46.4 (3.8)	40.5 (1.7)
Never	50.8 (1.6)	46.0 (3.7)	51.6 (1.7)
Systolic blood pressure (mmHg)	126.3 (0.6)	127.0 (1.5)	126.1 (0.6)
BMI (kg/m^2)	28.9 (0.2)	31.6 (0.5)	28.4 (0.2)
Total cholesterol (mg/dL)	193.0 (1.3)	173.4 (3.4)	196.6 (1.3)
HDL cholesterol (mg/dL)	50.0 (0.5)	44.4 (1.0)	51.0 (0.5)
C-reactive protein (mg/L)	1.9 [1.0,4.4]	1.7 [0.9,3.6]	2.0 [1.0,4.4]

Data are weighted means (SE), weighted median [IQR], or weighted proportions (SE).

Other variables of interest

Other measurement protocols in ARIC CARMRI were identical to those implemented in the original ARIC Study (7). Blood samples were assayed for total and high-density lipoprotein cholesterol, glucose, and high-sensitivity C-reactive protein using conventional techniques. BMI was computed from measured height and weight. Information on cigarette smoking and alcohol consumption was elicited during the interview. Resting systolic blood pressure (average of two readings) was measured using a random-zero sphygmomanometer. Participants were asked to bring current medications to the visit, and information on cholesterol- and blood pressure-lowering medications was also obtained during the interview. Diabetes history was determined by use of glucose-lowering medications or a self-reported physician diagnosis of diabetes. Previous history of coronary heart disease included a reported history of coronary heart disease and/or an adjudicated coronary heart disease event during active surveillance up to the CARMRI visit (14).

Statistical analysis

Characteristics of the study population were calculated overall and by history of diagnosed diabetes. We also compared mean values of each glycemic marker by categories of important risk factors separately in people with and without a history of diagnosed diabetes. We used multivariable logistic regression models to assess the independent association of each glycemic marker with microvascular conditions: chronic kidney disease, albuminuria, and retinopathy. For comparability, we divided the population into diabetes-specific tertiles of each glycemic marker. Because 1,5-AG is lowered while the other glycemic markers are increased in the setting of hyperglycemia, we transformed 1,5-AG to 1/1,5-AG for consistency in interpretation of the diabetes-specific tertiles (the ranking of individuals is unchanged by inverse transformation). Model 1 was adjusted for age (in years), sex, education level (less than high school; high school or equivalent; some college or higher), family history of diabetes, previous history of coronary heart disease, average systolic blood pressure (in mmHg), use of blood pressure medication, use of cholesterol-lowering medication, total cholesterol concentration (in mg/dL), HDL cholesterol concentration (in mg/dL), smoking status (current; former; never), BMI (in kg/m^2), and high-sensitivity C-reactive protein concentration (in mg/L). Because there is ongoing debate regarding the need for correction of fructosamine assays for serum albumin (15), models of fructosamine were additionally adjusted for serum albumin concentration

Table 2—*Mean levels of glycemic markers by demographic and clinical characteristics in participants without a history of diabetes (n = 1,323)*

	Glycated albumin (%)	Fructosamine (μmol/L)	1,5-AG (μg/mL)	HbA_{1c} (%)	Fasting glucose (mg/dL)
Overall	13.6 (0.05)	230.1 (0.7)	17.9 (0.2)	5.6 (0.02)	102.7 (0.5)
Age (years)					
<65	13.3 (0.1)	227.5 (0.9)	19.1 (0.6)	5.6 (0.04)	103.0 (1.5)
≥65	13.7 (0.05)	230.7 (0.8)	17.6 (0.8)	5.6 (0.02)	102.6 (0.7)
P value	0.01	0.12	0.01	0.47	0.83
Sex					
Women	13.6 (0.1)	229.8 (0.9)	17.3 (0.3)	5.7 (0.03)	101.0 (0.7)
Men	13.5 (0.1)	230.6 (1.1)	18.6 (0.4)	5.6 (0.02)	105.1 (0.9)
P value	0.34	0.58	0.005	0.02	<0.001
Race					
White	13.4 (0.1)	228.5 (0.8)	18.0 (0.3)	5.6 (0.1)	102.0 (0.6)
Black	14.6 (0.1)	238.6 (0.2)	17.1 (0.4)	5.9 (0.1)	106.3 (1.1)
P value	<0.001	<0.001	0.0627	<0.001	0.001
Education					
<12 years	13.9 (0.1)	234.2 (1.8)	18.8 (0.5)	5.7 (0.1)	104.1 (1.5)
High school or equivalent	13.7 (0.1)	231.1 (1.1)	17.8 (0.4)	5.6 (0.02)	103.3 (0.9)
Tertiary education	13.4 (0.1)	227.8 (1.1)	17.6 (0.3)	5.6 (0.03)	101.6 (0.7)
P value for trend	0.001	0.001	0.11	0.24	0.07
Family history of diabetes					
No	13.6 (0.6)	229.3 (0.8)	18.0 (0.2)	5.6 (0.02)	102.1 (0.6)
Yes	13.8 (0.1)	233.4 (1.8)	17.4 (0.5)	5.7 (0.04)	105.1 (1.3)
P value	0.12	0.04	0.33	0.52	0.04
History of coronary heart disease					
No	13.6 (0.1)	230.1 (0.8)	17.8 (0.2)	5.6 (0.02)	102.8 (0.6)
Yes	13.5 (0.1)	230.1 (2.2)	18.2 (0.8)	5.5 (0.04)	101.8 (1.4)
P value	0.48	0.98	0.64	0.01	0.55
Hypertension					
No	13.5 (0.1)	228.5 (1.1)	17.9 (0.4)	5.6 (0.03)	100.0 (0.9)
Yes	13.6 (0.1)	230.9 (0.9)	17.8 (0.3)	5.7 (0.02)	104.0 (0.7)
P value	0.24	0.10	0.80	0.004	<0.001
Hypercholesterolemia					
No	13.7 (0.1)	230.2 (1.0)	17.9 (0.3)	5.6 (0.3)	102.0 (0.8)
Yes	13.5 (0.1)	230.1 (1.0)	17.8 (0.3)	5.7 (0.2)	103.5 (0.8)
P value	0.03	0.94	0.76	0.21	0.21
Smoking					
Current	13.0 (0.1)	222.5 (2.4)	19.6 (0.9)	5.6 (0.05)	101.0 (2.2)
Former	13.5 (0.1)	230.5 (1.2)	17.9 (0.4)	5.6 (0.03)	102.9 (0.9)
Never	13.7 (0.7)	231.0 (1.0)	17.6 (0.3)	5.7 (0.03)	102.8 (0.7)
P value for trend	<0.001	0.02	0.05	0.31	0.64
BMI (kg/m^2)					
<25	14.0 (0.1)	235.1 (1.2)	16.5 (0.5)	5.6 (0.05)	98.3 (1.1)
25 to <30	13.5 (0.1)	230.0 (1.0)	18.0 (0.3)	5.6 (0.02)	101.7 (0.8)
≥30	13.4 (0.1)	226.6 (1.4)	18.7 (0.4)	5.7 (0.03)	107.4 (1.0)
P value for trend	<0.001	<0.001	0.001	0.005	<0.001
C-reactive protein (mg/L)					
<1	13.8 (0.1)	233.5 (1.3)	17.5 (0.4)	5.6 (0.05)	100.0 (1.0)
1 to <3	13.4 (0.1)	229.0 (1.2)	17.7 (0.4)	5.6 (0.03)	101.3 (0.9)
≥3	13.7 (0.1)	229.0 (1.3)	18.3 (0.4)	5.7 (0.02)	106.0 (0.9)
P value for trend	0.64	0.02	0.18	0.14	<0.001
Chronic kidney disease (eGFR <60 mL/min/1.73 m^2)					
No	13.5 (0.1)	229.0 (0.8)	17.8 (0.2)	5.6 (0.02)	102.5 (0.6)
Yes	13.9 (0.1)	235.1 (1.9)	18.0 (0.6)	5.7 (0.05)	103.5 (1.5)
P value	0.01	0.003	0.82	0.03	0.56

Table 2—*Continued*

	Glycated albumin (%)	Fructosamine (μmol/L)	1,5-AG (μg/mL)	HbA_{1c} (%)	Fasting glucose (mg/dL)
Albuminuria					
No	13.5 (0.05)	229.4 (0.7)	18.0 (0.2)	5.6 (0.02)	102.2 (0.6)
Yes	14.1 (0.2)	236.3 (2.6)	16.7 (0.6)	5.8 (0.1)	107.2 (2.0)
P value	0.01	0.01	0.05	0.02	0.02
Retinopathy*					
No	13.6 (0.05)	229.8 (0.7)	17.9 (0.2)	5.6 (0.02)	102.7 (0.6)
Yes	14.2 (0.3)	235.7 (5.8)	17.1 (1.4)	5.9 (0.2)	99.4 (2.3)
P value	0.03	0.32	0.59	0.21	0.16

Data are weighted means (SE). *n = 1,284.

(in g/dL). Model 2 was adjusted for all variables in model 1 plus HbA_{1c} (in percentages). All analyses were weighted by the inverse of the sample fractions in the study sampling strata using methods for the analysis of complex sample survey design data (7).

All reported *P* values are two-sided, and *P* values <0.05 were considered statistically significant.

RESULTS—The prevalence estimates for each the microvascular conditions in people with a history of diabetes were as follows: 27.7% had chronic kidney disease, 23.0% had albuminuria (4.1% macroalbuminuria), and 11.4% had retinopathy. In people without a history of diabetes, the corresponding prevalence estimates were 18.1% for chronic kidney disease, 10.4% for albuminuria (0.9% macroalbuminuria), and 2.8% for retinopathy. Demographic and clinical variables also differed substantially by diabetic status (Table 1). People with a history of diagnosed diabetes were more likely to be men and African American and have a high-school education or less and a family history of diabetes compared with people in the study sample with no history of diabetes. People with diagnosed diabetes also had poorer cardiovascular risk profiles and were less likely to be current smokers.

Mean levels of the different glycemic markers differed substantially by diabetic status (Tables 2 and 3). The mean glycated albumin, fructosamine, 1,5-AG, HbA_{1c}, and fasting glucose values in people without a history of diagnosed diabetes were 13.6%, 230.1 μmol/L, 17.9 μg/mL, 5.6%, and 102.7 mg/dL, respectively. In people with diabetes, the corresponding means were 17.8%, 274.3 μmol/L, 12.6 μg/mL, 6.7%, and 140.1 mg/dL, respectively. Table 2 reveals substantial differences in the associations of each marker with basic demographic and clinical characteristics. In people without diabetes, glycated albumin was significantly higher and 1,5-AG was lower in people aged 65 years and older compared with people <65 years of age; fructosamine, HbA_{1c}, and fasting glucose did not differ by age group. Whereas fructosamine and glycated albumin appeared similar by sex, men had significantly higher 1,5-AG, higher HbA_{1c}, and higher fasting glucose. BMI was significantly associated with all markers but not in the expected direction for glycated albumin or fructosamine, which were both lower, and for 1,5-AG, which was higher, at higher BMI levels. By contrast, HbA_{1c} and fasting glucose were both significantly higher at higher BMI levels. Levels of glycated albumin and fructosamine were also significantly higher in people who have never smoked compared with former or current smokers. HbA_{1c} and fasting glucose were not significantly different across categories of smoking. Substantial racial differences were seen across all markers in both people with and without diabetes, with African Americans having higher levels of glycemia as indicated by each marker, although the results were not statistically significant for 1,5-AG in people with or without diabetes. Fasting glucose was higher, but not statistically significantly so, in diabetic African Americans compared with whites (*P* value = 0.13). In these unadjusted analyses, we observed associations between some of the glycemic markers and prevalent chronic kidney disease, albuminuria, and retinopathy, but these results were variable across the different measures of hyperglycemia (Tables 2 and 3).

In our adjusted logistic regression models of microvascular outcomes in the total population comparing diabetes-specific tertiles of each glycemic marker, we observed significant positive trends in the associations of each marker with albuminuria and retinopathy (Fig. 1 and Supplementary Table 1), even after accounting for demographic, clinical, and lifestyle factors. The associations with chronic kidney disease were similar in magnitude and direction but not significant for all markers: glycated albumin (*P* trend = 0.005), fructosamine (*P* trend = 0.003), and HbA_{1c} (*P* trend = 0.005) were significantly and positively associated with the presence of chronic kidney disease, but 1/1,5-AG (*P* trend = 0.72) and fasting glucose (*P* trend = 0.66) were not. After further adjustment for HbA_{1c} in these models (Supplementary Fig. 1 and Supplementary Table 2), we observed significant trends in the associations of glycated albumin with retinopathy (*P* trend = 0.01) and borderline significant trends for chronic kidney disease (*P* trend = 0.05) and albuminuria (*P* trend = 0.07). After adjustment for HbA_{1c}, positive trends for fructosamine also remained significant for chronic kidney disease (*P* trend = 0.03) and retinopathy (*P* trend = 0.02) and borderline significant for albuminuria (*P* trend = 0.05). 1/1,5-AG remained significantly positively associated with albuminuria (*P* trend = 0.04) but not with chronic kidney disease (*P* trend = 0.63) or retinopathy (*P* trend = 0.42). Overall trends for fasting glucose were not significant for any outcome after adjustment for HbA_{1c} (all *P* trends >0.3); however, the lowest tertile of fasting glucose in people with diagnosed diabetes was significantly associated with chronic kidney disease and albuminuria. HbA_{1c}, by contrast, was no longer statistically significantly associated with any of these outcomes in these fully adjusted models (all *P* values >0.05).

CONCLUSIONS—We compared nontraditional serum markers of glycemia (glycated albumin, fructosamine, and

Table 3—*Mean levels of glycemic markers by demographic and clinical characteristics in participants with diagnosed diabetes* (n = 277)

	Glycated albumin (%)	Fructosamine (μmol/L)	1,5-AG (μg/mL)	HbA_{1c} (%)	Fasting glucose (mg/dL)
Overall	17.8 (0.3)	274.3 (3.4)	12.6 (0.6)	6.7 (0.1)	140.1 (3.0)
Age (years)					
<65	18.7 (0.9)	284.2 (8.8)	10.7 (1.4)	7.2 (0.3)	151.6 (7.0)
≥65	17.6 (0.3)	272.4 (3.7)	12.9 (0.6)	6.7 (0.1)	137.8 (3.3)
P value	0.28	0.23	0.13	0.06	0.08
Sex					
Women	17.7 (0.4)	270.0 (4.7)	13.2 (0.9)	6.8 (0.1)	145.6 (4.4)
Men	17.9 (0.5)	279.0 (5.2)	11.9 (0.8)	6.7 (0.1)	134.1 (4.1)
P value	0.66	0.22	0.24	0.71	0.06
Race					
White	16.8 (0.3)	264.6 (3.7)	13.3 (0.7)	6.5 (0.1)	136.6 (3.3)
Black	19.9 (0.7)	295.1 (7.3)	11.1 (0.9)	7.2 (0.2)	147.4 (6.3)
P value	<0.001	<0.001	0.08	<0.001	0.13
Education					
<12 years	19.3 (0.8)	296.4 (9.6)	11.0 (1.2)	7.2 (0.2)	147.6 (7.5)
High school or equivalent	17.5 (0.4)	269.1 (5.0)	13.5 (0.9)	6.6 (0.1)	136.5 (4.5)
Tertiary education	17.4 (0.5)	269.2 (5.2)	12.2 (0.8)	6.7 (0.1)	141.0 (4. 8)
P value for trend	0.06	0.03	0.61	0.05	0.60
Family history of diabetes					
No	17.8 (0.4)	275.6 (4.6)	13.1 (0.7)	6.7 (0.1)	136.4 (3.7)
Yes	17.8 (0.5)	272.2 (5.5)	11.8 (1.0)	6.7 (0.1)	146.2 (5.1)
P value	0.97	0.65	0.29	0.99	0.12
History of coronary heart disease					
No	17.8 (0.3)	273.9 (3.7)	12.7 (0.6)	6.7 (0.1)	140.3 (3.3)
Yes	17.9 (0.9)	276.4 (9.3)	12.1 (1.5)	6.9 (0.3)	138.9 (8.2)
P value	0.93	0.81	0.70	0.44	0.87
Hypertension					
No	17.0 (1.0)	263.0 (10.1)	12.7 (1.5)	6.5 (0.2)	139.0 (7.5)
Yes	17.9 (0.3)	275.9 (3.6)	12.6 (0.6)	6.8 (0.1)	140.2 (3.3)
P value	0.36	0.24	0.94	0.19	0.88
Hypercholesterolemia					
No	19.4 (0.7)	291.3 (8.4)	11.3 (1.1)	7.0 (0.2)	148.6 (6.4)
Yes	17.3 (0.3)	268.6 (3.6)	13.0 (0.7)	6.7 (0.1)	137.2 (3.4)
P value	0.01	0.02	0.16	0.06	0.12
Smoking					
Current	18.1 (1.0)	263.9 (12.1)	12.2 (2.1)	6.6 (0.2)	140.1 (8.5)
Former	17.6 (0.5)	274.5 (5.5)	11.6 (0.7)	6.7 (0.1)	136.7 (4.1)
Never	18.0 (0.4)	275.9 (4.9)	13.7 (1.0)	6.8 (0.1)	143.5 (5.0)
P value for trend	0.78	0.49	0.17	0.65	0.39
BMI (kg/m^2)					
<25	19.5 (0.8)	294.6 (10.9)	11.7 (1.4)	6.6 (0.1)	141.8 (7.6)
25 to <30	16.9 (0.5)	265.3 (6.3)	11.7 (0.8)	6.6 (0.2)	127.5 (4.7)
≥30	17.8 (0.4)	273.7 (4.4)	13.2 (0.9)	6.9 (0.1)	145.5 (4.2)
P value for trend	0.33	0.26	0.24	0.09	0.18
C-reactive protein (mg/L)					
<1	17.6 (0.4)	275.4 (5.1)	12.4 (1.0)	6.5 (0.1)	135.9 (5.5)
1 to <3	17.8 (0.5)	274.6 (5.9)	11.9 (0.9)	6.7 (0.1)	137.0 (4.6)
≥3	17.9 (0.6)	273.0 (6.9)	13.6 (1.1)	7.0 (0.2)	148.2 (5.7)
P value for trend	0.69	0.79	0.44	0.02	0.11
Chronic kidney disease (eGFR <60 mL/min/1.73 m^2)					
No	17.9 (0.3)	275.1 (4.0)	11.9 (0.6)	6.8 (0.1)	141.4 (3.4)
Yes	17.6 (0.7)	272.3 (7.4)	14.3 (1.4)	6.6 (0.1)	136.7 (6.5)
P value	0.76	0.74	0.13	0.21	0.53
Albuminuria					
No	17.3 (0.3)	268.6 (3.7)	13.0 (0.7)	6.7 (0.1)	139.3 (3.0)
Yes	19.4 (0.7)	293.4 (8.8)	11.1 (1.1)	7.0 (0.2)	142.7 (7.9)
P value	0.01	0.01	0.16	0.04	0.69

Table 3—*Continued*

	Glycated albumin (%)	Fructosamine (μmol/L)	1,5-AG (μg/mL)	HbA_{1c} (%)	Fasting glucose (mg/dL)
Retinopathy*					
No	17.3 (0.3)	268.6 (3.4)	12.8 (0.6)	6.7 (0.1)	136.9 (3.0)
Yes	20.9 (1.3)	306.8 (14.4)	11.4 (1.8)	7.2 (0.3)	163.6 (12.7)
P value	0.01	0.01	0.45	0.09	0.04

Data are weighted means (SE). *n = 265.

1,5-AG) to the standard measures used in clinical practice (fasting glucose and HbA_{1c}) in their associations with microvascular conditions. We observed intriguing differences in the associations of each glycemic marker with basic demographic and clinical characteristics. To the extent that cross-sectional risk factor associations differ, this may indicate that the different glycemic markers contribute independent clinical information and may enhance the prognostic value of standard glycemic markers. Indeed, we observed qualitative differences in the associations of the various glycemic markers with smoking status and BMI. There is evidence that both smoking and higher levels of adiposity can lead to a state of increase oxidative stress because of increased reactive oxygen species (16). Our data may indicate that circulating concentrations of glycated albumin and fructosamine are differentially affected by these states of oxidant stress compared with traditional glycemic markers. It is also possible that glycated albumin, fructosamine, and 1,5-AG are more strongly affected by postprandial glycemic excursions compared with HbA_{1c}, contributing to the observed differences (17,18).

After adjustment for confounding factors, we found that glycated albumin, fructosamine, and HbA_{1c} were similarly positively associated with prevalent chronic kidney disease, albuminuria, and retinopathy. Fasting glucose and 1,5-AG were associated with albuminuria and retinopathy but not chronic kidney disease. The associations of glycated albumin and fructosamine with microvascular outcomes were evident even after adjustment for HbA_{1c}, suggesting that these serum markers of glycemic control may contribute independent risk information. The less robust results for fasting glucose, particularly among people with a diagnosis of diabetes in the upper two tertiles of the glycemic markers, may partially reflect that nearly all people with diagnosed diabetes reported current use of glucose-lowering medication(s).

Fructosamine is often used in clinical practice to monitor glycemic control in people with conditions that interfere with

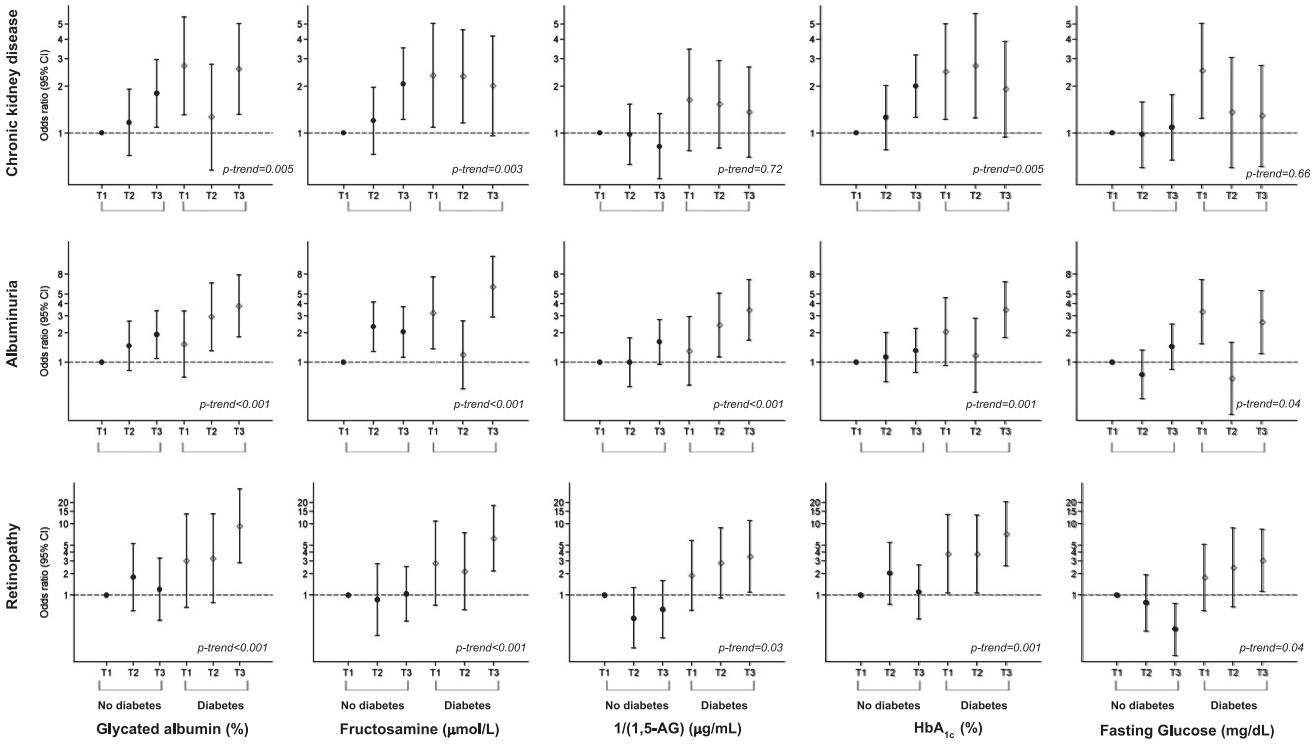

Figure 1—*Adjusted odds ratios (95% CI) for microvascular conditions by diabetes-specific tertiles of each glycemic marker; odds ratios are adjusted for age, sex, education level, family history of diabetes, previous coronary heart disease, use of blood pressure medication, use of cholesterol-lowering medication, smoking status, BMI, systolic blood pressure, total cholesterol, HDL cholesterol, and C-reactive protein. Fructosamine models are additionally adjusted for serum albumin. Chronic kidney disease was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2.*

the interpretation or measurements of HbA_{1c}, such as the presence of some hemoglobin variants, certain anemias, dialysis treatment, or other conditions that cause hemolysis or otherwise alter erythrocyte turnover. The colorometric process of the fructosamine assay is challenging to perform, and there is ongoing debate regarding the need for correction of fructosamine assays for serum albumin concentrations (15,19). For this reason, we adjusted all fructosamine analyses for serum albumin concentration. An additional general concern regarding fructosamine is the fluctuating concentrations of other serum proteins that may affect the assay result. Our study demonstrates excellent reliability of this fructosamine assay with an interassay CV = 3.7% and significant associations of fructosamine with microvascular outcomes. The glycated albumin assay examined here is a newer automated assay not yet approved for clinical use in the U.S. but which also showed excellent laboratory performance, interassay CV = 2.7%. In this assay, glycated albumin is expressed as a percentage of total serum albumin (20), simplifying the interpretation of the result. Indeed, additional adjustment for serum albumin in our analyses of glycated albumin and microvascular outcomes did not appreciably alter our results (data not shown). It has also been suggested that glycated albumin itself, beyond its role as marker of hyperglycemia, may contribute directly to the development of complications (21), including diabetic nephropathy (22,23).

1,5-AG is a novel marker of glycemia, reflecting a nonglycation-dependent biological process: it is thought to reflect hyperglycemic excursions over the past 1 to 2 weeks (4). Urinary excretion of 1,5-AG is accelerated in the setting of hyperglycemia and high circulating concentrations of glucose (exceeding the renal threshold) will cause serum 1,5-AG concentrations to fall (24). The attractiveness of 1,5-AG is that it may capture additional information on glycemic excursions not reflected in fasting glucose, HbA_{1c}, fructosamine, or glycated albumin values (17). However, it is unclear whether concentrations of 1,5-AG may be altered in the presence of moderately impaired kidney function or albuminuria, raising questions regarding reverse causality.

Limitations that should be considered in the interpretation of these data include the cross-sectional design; we could not determine the temporality of the observed associations, and we had only a limited number of people with known diabetes (N = 277). Sample size limitations excluded the possibility of comprehensive examination of other subgroups. The direct comparison between results for glycated albumin versus those for fructosamine remains challenging. To our knowledge, there is no reference method procedure for glycated albumin or for those measurements related to glycation of proteins circulating in blood. Thus, the fructosamine assay (a colorimetric assay based on ketoamines reducing nitrotetrazolium-blue) does not directly relate to the measure of glycated albumin (an enzymatic method using ketoamine oxidase and an albumin-specific protease), and differences in results across these measurements are difficult to interpret in the context of an epidemiologic study. Important strengths of this study include the comparison of a panel of novel serum markers with those that are used in standard practice, the community-based biracial sample of people with and without diabetes, which allowed us to assess these epidemiologic associations across the full range of glycemia. Additional advantages to conducting this study nested within the ARIC cohort included the rigorous measurement of known risk factors for diabetes using standardized protocols and assessment of multiple microvascular conditions. We observed excellent laboratory performance for all assays.

Physicians typically use multiple biomarkers to assess the metabolic status of their patients, but the additional clinical utility of serum glycemic markers beyond standard measures of glycemia is unclear. In our cross-sectional analyses, two serum markers of glycemia—glycated albumin and fructosamine—were as strongly, or more strongly, associated with microvascular conditions as HbA_{1c}. Our results suggest that serum glycemic markers, particularly glycated albumin and/or fructosamine, may add important clinical information for the identification of people at risk for microvascular conditions and possibly the management of diabetes. Measurement of HbA_{1c} requires a whole-blood sample; sometimes relatively labor-intensive assay methodologies and concerns have been raised about the performance of HbA_{1c} in certain subpopulations (25). The markers examined here can be measured reliably in serum using standard, automated methods and may be useful in settings where whole blood is not available. Whether serum glycemic markers might complement or outperform HbA_{1c} in terms of long-term predictive value requires further investigation.

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E.S. collected and analyzed the data and wrote the article. L.M.A.F. analyzed the data and reviewed the article. C.M.B. reviewed the article and contributed to the discussion. R.C.H., J.C., and F.L.B. reviewed and edited the article and contributed to the discussion. M.W.S. collected the data and reviewed and edited the article and contributed to the discussion.

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