Alternative Markers of Hyperglycemia and Risk of Diabetes

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OBJECTIVE—Fructosamine, glycated albumin, and 1,5-anhydroglucitol (1,5-AG) are of interest for monitoring short-term glycemic control in patients with diabetes; however, their associations with diabetes risk are uncharacterized.

RESEARCH DESIGN AND METHODS—We used Cox proportional hazards models to examine the associations of fructosamine, glycated albumin, and 1,5-AG with incident diabetes in 1,299 participants, from the Atherosclerosis Risk in Communities (ARIC) Study (2005–2006), who had no history of diagnosed diabetes at baseline. Incident diabetes was self-reported during annual telephone calls.

RESULTS—There were 119 new cases of diabetes during a median follow-up of 3.3 years. When compared with the lowest quartile, the fourth quartiles of fructosamine and glycated albumin were significantly associated with diabetes risk (hazard ratio [HR] 3.99 [95% CI 1.93–8.28] and 5.22 [2.49–10.94], respectively). The fourth quartile of 1,5-AG was associated with a significantly lower diabetes risk (0.27 [0.14–0.55]). Associations were attenuated but still significant after adjustment for hemoglobin A_{1c} (A1C) or fasting glucose.

CONCLUSIONS—Fructosamine, glycated albumin, and 1,5-AG were associated with the subsequent development of diabetes independently of baseline A1C and fasting glucose. Our results suggest these alternative biomarkers may be useful in identifying persons at risk for diabetes.

Nontraditional serum markers of short-term glucose control may enhance our ability to monitor hyperglycemia in persons with diabetes. Fructosamine, glycated albumin, and 1,5-anhydroglucitol (1,5-AG) have been of recent interest, particularly for use in populations in which interpretation of glycated hemoglobin (A1C) may be problematic (1–3), such as in the setting of anemia, hemolysis, or renal disease (4–6). Fructosamine is produced when blood glucose forms ketoamines by covalently binding to serum proteins (7). Similarly, glycated albumin is formed via glycation of serum albumin (1). 1,5-AG is a serum monosaccharide that is excreted in the urine at an accelerated rate in the presence of glycosuria (2). Whereas fructosamine and glycated albumin increase in the presence of hyperglycemia, 1,5-AG decreases in the setting of elevated circulating glucose concentrations (1,7). The 1,5-AG is approved by the Food and Drug Administration for short-term monitoring of glycemic control in persons with diabetes and has been suggested for use in monitoring postprandial hyperglycemia (8,9).

Despite growing interest in fructosamine, glycated albumin, and 1,5-AG for monitoring short-term glycemic control (3,10,11), few studies have measured these novel serum measures in initially nondiabetic populations. It is unknown if they are associated with the future diagnosis of diabetes. It is also unknown if these markers provide distinct information apart from A1C or fasting glucose concentrations. The purpose of this study was to examine the relationships of fructosamine, glycated albumin, and 1,5-AG with the risk of diagnosed diabetes and to determine if the associations were independent of baseline A1C or fasting glucose.

RESEARCH DESIGN AND METHODS

Study population
The Atherosclerosis Risk in Communities (ARIC) Study is a community-based prospective cohort of 15,792 adults originally enrolled from 1987 to 1989 from four United States communities and followed-up for more than two decades (12,13). In 2005–2006, 2,045 ARIC participants were selected via a stratified sampling plan for participation in the Carotid Magnetic Resonance Imaging substudy (CARMRI) (14). Physical examinations, medical interviews, and laboratory tests were conducted as part of the CARMRI clinical visit. Our study population was limited to the 1,299 participants who did not have a diagnosis of diabetes at the 2005–2006 CARMRI visit (hereafter called baseline), who were fasting ≥8 hours, who had valid measurements of A1C, fasting glucose, fructosamine, glycated albumin, and 1,5-AG, who were not missing case status information, and who were not missing relevant covariate data at baseline. Baseline diabetes status was determined by self-reported physician diagnosis of diabetes or use of glucose-lowering medications.

Written informed consent was obtained from all participants, and the study protocol was approved by Institutional Review Boards at all clinical sites.

Glycemic markers
The A1C and glucose were measured in 2005–2006 as part of the CARMRI protocol using a Roche Hitachi 911 Analyzer. The A1C was measured using a Tinaquant II immunoassay method (Roche Diagnostics, Basel, Switzerland) and calibrated to the Diabetes Control and Complications Trial assay. Glucose was

measured in serum using the hexokinase method (Roche Diagnostics).

Fructosamine (Roche Diagnostics), glycated albumin (and albumin) (Lucica GA-L; Asahi Kasei Pharma Corporation, Tokyo, Japan), and 1,5-AG (GlycoMark, Winston-Salem, NC) were measured in 2009 from stored serum samples using a Roche Modular P800 system (Roche Diagnostics). Per the manufacturer's instructions, glycated albumin was expressed as a percentage of total serum albumin, i.e., [(glycated albumin)/(serum albumin) $\times 100/1.14 + 2.9$]. The interassay coefficients of variation were 3.7 (fructosamine), 2.7 (glycated albumin), and 4.8% (1,5-AG). Reference intervals were 10 to 1,000 μmol/L (fructosamine), 0 to 24.0% (glycated albumin), and 6.8 to 32.0 μg/mL (1,5-AG).

Incident diabetes

Cases of incident diabetes were identified from self-reported information obtained during annual telephone calls to all ARIC participants. The ARIC participants were contacted every year on the approximate anniversary of their initial ARIC examination. Annual telephone follow-up response rates are high in ARIC and averaged >90% during the time of this study. Among persons with no self-reported history of diabetes and no diabetes medication use, we identified new cases of diabetes between the baseline CARMRI visit (2005–2006) and April 18, 2011 (the last date of telephone follow-up available at the time of this study). Participants were considered an incident case of diabetes on the date of their first "yes" response to glucose-lowering medication use or the following questions: "Has a doctor ever said you have diabetes or sugar in the blood?" (2006–February 7, 2008) or "Since we last contacted you, has a doctor said you have diabetes or sugar in the blood?" (February 7, 2008–April 18, 2011). Date of self-report was used as a surrogate for the date of diagnosis. Self-reported diabetes previously has been shown to be a valid measurement of diabetes in this study population (15,16). Administrative censoring occurred on the date of last response to the annual follow-up survey.

Other variables of interest

Trained study personnel collected all data using standardized protocols with extensive quality control and assurance measures, as described previously (14). Age, sex, race, parental history of diabetes, and smoking status were self-reported. Systolic blood pressure was calculated from the mean of three measurements obtained with a random-zero sphygmomanometer. Total cholesterol and HDL were measured enzymatically in serum.

Statistical analyses

We calculated the crude 3-year cumulative incidence of diabetes (Kaplan-Meier method) by quartiles of each glycemic marker at baseline. We utilized Cox proportional hazard models to examine the independent associations of baseline categories (quartiles) of fructosamine, glycated albumin, and 1,5-AG with risk of incident diagnosed diabetes. Model 1 was adjusted for age, gender, race, total cholesterol, HDL cholesterol, BMI, mean systolic blood pressure, parental family history of diabetes, and smoking status. Model 2a was adjusted for all variables in Model 2 plus baseline fasting glucose. Model 2b was adjusted for all variables in Model 2 plus baseline A1C. To evaluate the continuous associations between each marker and diabetes risk, we used Cox proportional hazards models and restricted cubic splines (17) with knots specified at the 25th, 50th, and 75th percentiles. Spline models were centered at the 25th percentile and truncated at the 1st and 99th percentiles for all markers. We also conducted analyses of quartiles of fructosamine, glycated albumin, and 1,5-AG stratified by baseline categories of fasting glucose (<100 mg/dL and 100–125 mg/dL) or A1C (<5.7 and 5.7–6.4%) to see if any associations of alternative markers of glycemia with incident diabetes persisted among persons with glucose or A1C levels in the normal or prediabetic ranges. Pearson correlation coefficients (r) were calculated to describe linear relationships between fructosamine, glycated albumin, 1,5-AG, A1C, and fasting glucose.

All analyses were conducted using Stata 11.1 (StataCorp LP, College Station, TX) and weighted to account for the CARMRI sampling design (14). Standard errors were estimated using the Taylor series (linearization) method.

RESULTS—The study population (Table 1) was 42% male and 18% black, with a mean age of 70 years (SE 0.2), and 8% (SE 0.9) were current cigarette smokers. In this community-based population of persons without diagnosed diabetes at baseline, the mean fasting glucose was 102.0 mg/dL (SE 0.5), and mean A1C

Table 1—Characteristics of the study population (N = 1,299)

Characteristics	
Age, years	70.2 (0.2)
Male (%)	41.9 (1.7)
Black (%)	17.9 (0.003)
BMI (kg/m^2)	28.4 (0.2)
Total cholesterol (mg/dL)	197.9 (1.3)
HDL cholesterol (mg/dL)	51.4 (0.5)
Systolic blood pressure (mmHg)	126.3 (0.7)
Smoking status (%)	
Current	7.9 (0.9)
Former	39.3 (1.7)
Never	52.8 (1.7)
Parental history of diabetes (%)	20.6 (1.4)
Hemoglobin A$_{1c}$ (%)	5.6 (0.02)
Fasting glucose (mg/dL)	102.0 (0.5)
Fructosamine (μmol/L)	229.7 (0.7)
Glycated albumin (%)	13.6 (0.1)
1,5-AG (μg/mL)	18.0 (0.2)

Estimates are weighted means (SE) or proportions (SE).

was 5.6% (SE 0.02). There were 119 cases of incident diagnosed diabetes during a median of 3.3 years of follow-up (range, 1.3 months to 5.7 years). Pearson correlation coefficients of fasting glucose or A1C with fructosamine, glycated albumin, and 1,5-AG are provided as a Supplementary Table 1.

The overall crude 3-year cumulative incidence of diabetes (Kaplan-Meier method) was 8.5%. The 3-year cumulative incidence estimates for risk of diabetes by baseline quartiles of each of the serum markers of glycemic control are shown in Table 2. The hazard ratios (HRs) from our adjusted Cox proportional hazards models are also shown in Table 2. Higher baseline quartiles of fructosamine and glycated albumin were associated with a significantly higher risk of diabetes in a dose–response manner, even after adjustment for traditional risk factors (Model 2a). After additional adjustment for fasting glucose or A1C, these trends remained significant and the HRs were strongly positive (Model 2b). Higher baseline quartiles of 1,5-AG were inversely associated with incident diabetes in a dose–response manner, even after adjusting for diabetes risk factors and fasting glucose or A1C. Fasting glucose was the most strongly associated with incident diagnosed diabetes even after adjustment for A1C. The pattern of association of

Table 2—*Three-year cumulative incidence and adjusted HRs (95% CIs) of incident diagnosed diabetes by quartiles of glycemic markers at baseline (N = 1,299)*

	Quartile of fructosamine (μmol/L)				*P* for trend*
	163.1–216.1	216.2–228.0	228.2–241.3	241.4–463.4	
3-year cumulative incidence, %	5.1	5.9	10.2	12.8	
Crude	1.0 [Ref]	0.99 (0.43–2.29)	2.06 (1.04–4.08)	2.65 (1.35–5.20)	0.001
Model 1	1.0 [Ref]	1.30 (0.56–3.01)	2.85 (1.44–5.64)	3.99 (1.93–8.28)	<0.001
Model 2a	1.0 [Ref]	1.24 (0.53–2.87)	2.56 (1.32–4.99)	2.64 (1.31–5.35)	0.001
Model 2b	1.0 [Ref]	1.09 (0.45–2.64)	2.50 (1.25–4.99)	3.73 (1.80–7.74)	<0.001
	Quartile of glycated albumin (%)				
	9.7–12.6	12.7–13.4	13.5–14.4	14.5–34.8	
3-year cumulative incidence, %	6.3	5.5	6.8	15.7	
Crude	1.0 [Ref]	0.90 (0.40–2.04)	1.36 (0.66–2.78)	2.97 (1.54–5.71)	<0.001
Model 1	1.0 [Ref]	1.26 (0.56–2.81)	1.96 (0.94–4.09)	5.22 (2.49–10.94)	<0.001
Model 2a	1.0 [Ref]	1.21 (0.54–2.69)	1.74 (0.84–3.60)	3.28 (1.60–6.74)	0.001
Model 2b	1.0 [Ref]	1.27 (0.56–2.84)	1.79 (0.84–3.81)	4.61 (2.20–9.68)	<0.001
	Quartile of 1,5 AG (μg/mL)†				
	1.0–13.9	14.0–17.9	18.0–22.0	22.1–39.5	
3-year cumulative incidence, %	11.2	6.9	11.1	4.5	
Crude	1.0 [Ref]	0.61 (0.33–1.12)	0.97 (0.56–1.69)	0.39 (0.20–0.78)	0.024
Model 1	1.0 [Ref]	0.60 (0.33–1.11)	0.99 (0.56–1.73)	0.27 (0.14–0.55)	0.002
Model 2a	1.0 [Ref]	0.76 (0.40–1.45)	1.21 (0.67–2.19)	0.33 (0.16–0.67)	0.012
Model 2b	1.0 [Ref]	0.47 (0.23–0.95)	1.01 (0.58–1.74)	0.29 (0.15–0.58)	0.004
	Quartile of fasting glucose (mg/dL)				
	44.0–93.0	94.0–100.0	101.0–109.0	110.0–349.0	
3-year cumulative incidence, %	2.2	4.1	5.5	20.4	
Crude	1.0 [Ref]	1.59 (0.55–4.53)	2.91 (1.12–7.53)	8.85 (3.70–21.14)	<0.001
Model 1	1.0 [Ref]	1.53 (0.55–4.28)	2.36 (0.92–6.06)	6.88 (2.94–16.13)	<0.001
Model 2b	1.0 [Ref]	1.53 (0.54–4.28)	2.38 (0.93–6.12)	6.03 (2.55–14.26)	<0.001
	Quartile of hemoglobin A_{1c} (%)				
	3.3	5.4	8.6	16.7	
3-year cumulative incidence, %	3.3	5.4	8.6	16.7	
Crude	1.0 [Ref]	1.33 (0.57–3.07)	1.86 (0.90–3.83)	4.47 (2.33–8.57)	<0.001
Model 1	1.0 [Ref]	1.36 (0.59–3.14)	1.69 (0.83–3.42)	4.07 (2.03–8.16)	<0.001
Model 2a	1.0 [Ref]	1.34 (0.58–3.09)	1.44 (0.71–2.92)	2.60 (1.27–5.31)	0.007

Model 1 is adjusted for age, sex, race, total cholesterol, HDL cholesterol, BMI, average systolic blood pressure, parental history of diabetes, and smoking status. Model 2a includes all variables in Model 1 + baseline fasting glucose concentration. Model 2b includes all variables in Model 1 + baseline hemoglobin A_{1c}. *P value for trend evaluated using an ordinal variable based on the median value in each quartile. †Serum 1,5-AG is lowered in the presence of hyperglycemia. Higher concentrations at baseline thus were associated with a lower risk of diabetes.

A1C with incident diabetes was similar to that for fructosamine and glycated albumin. Comparison of the confidence intervals of the markers revealed no statistical difference across quartiles of fructosamine, glycated albumin, 1,5-AG, A1C, and fasting glucose in their associations with diabetes risk.

Figure 1 shows the continuous unadjusted associations of baseline fructosamine, glycated albumin, and 1,5-AG values with incident diabetes. Baseline values of fructosamine and glycated albumin were strongly and positively associated with subsequent risk of diagnosed diabetes. The magnitude of the associations was substantial (HRs >10.0 at high baseline values of fructosamine and glycated albumin). The observed associations were similar in magnitude for both fructosamine and glycated albumin. By contrast, 1,5-AG was inversely associated with incident diabetes and the magnitude of this association was weaker than that observed for fructosamine and glycated albumin.

In analyses limited to those persons with normal fasting glucose (<100 mg/dL) or A1C (<5.7%), fructosamine, glycated albumin, and 1,5-AG were no longer associated with incident diabetes (Table 3). However, when fasting glucose was between 100 and 125 mg/dL, significant positive trends were noted for both fructosamine (P trend = 0.03) and glycated albumin (P trend = 0.01). Similarly, when A1C was between 5.7 and 6.4%, both fructosamine and glycated albumin were significantly associated with incident diabetes (both P trends <0.001). 1,5-AG, however, was not significantly associated with incident diabetes in persons with fasting glucose <126 mg/dL or A1C <6.5%.

CONCLUSIONS—To our knowledge, this study represents one of the first reports of the associations of baseline

A

B

C
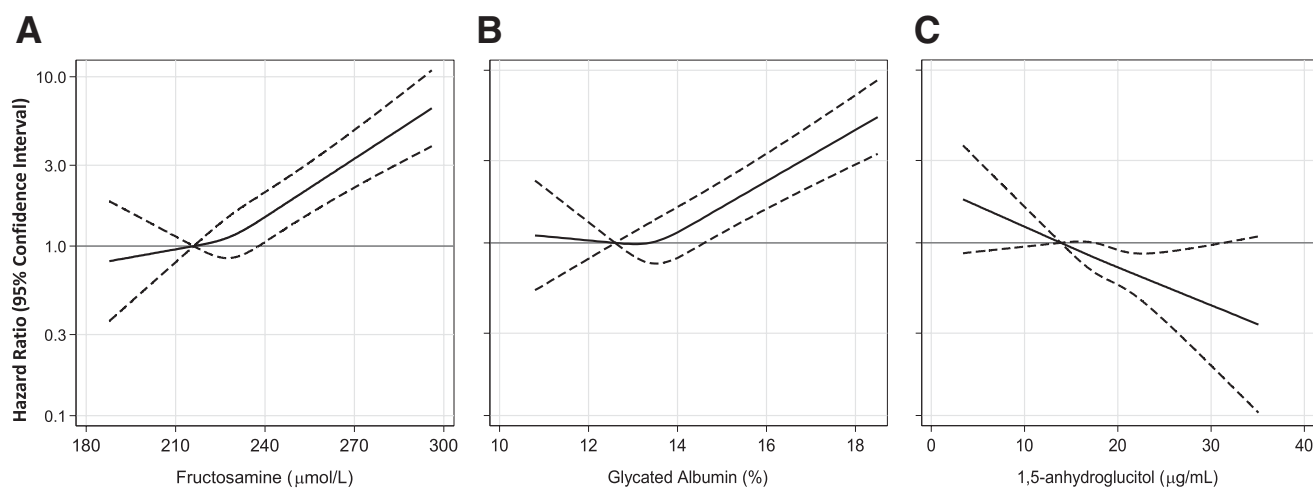
Figure 1—*Fructosamine* (A), *glycated albumin* (B), *and 1,5-AG* (C). *Unadjusted HRs* (solid line) *for self-reported diagnosed diabetes according to baseline concentrations of glycemic markers from restricted cubic spline models.* Dashed lines *are the 95% CIs. The models were expressed relative to the 25th percentile with knots specified at the 25th, 50th, and 75th percentiles. The plots were truncated at the 1st and 99th percentiles. The HRs are shown on a natural log scale.*

levels of fructosamine, glycated albumin, and 1,5-AG with the risk of diabetes. Overall, fructosamine and glycated albumin were strongly and similarly associated with incident diabetes in a dose–response manner. 1,5-AG is decreased in the setting of hyperglycemia and, consistent with its biology, baseline concentrations were inversely associated with diabetes risk. Interestingly, the observed associations for all three biomarkers persisted even after

adjustment for baseline A1C or fasting glucose, suggesting that these alternative markers of hyperglycemia may contribute independent information regarding diabetes risk. Furthermore, the associations of glycated albumin and fructosamine with incident diabetes were comparable with that for A1C.

Both fructosamine and glycated albumin are formed via nonenzymatic glycation reactions (1,7) and are elevated in the

setting of high circulating concentrations of glucose. Based on the rate of total serum protein and albumin turnover, these markers represent glycemia over a 2- to 3-week period (18,19). We observed that both fructosamine and glycated albumin were strongly associated with the subsequent risk of diabetes, and these associations remained significant after adjustment for fasting glucose or A_{1c}. For consistency with the common clinical

Table 3—*HRs (95% CIs) for risk of diagnosed diabetes by baseline categories of fasting glucose and A1C after excluding persons with undiagnosed diabetes*

	HR (95% CI) by quartile				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend*
Fasting glucose					
<100 mg/dL (N = 561)†					
Fructosamine	1.0 [Ref]	3.82 (0.71–20.69)	3.12 (0.63–15.49)	0.88 (0.15–5.31)	0.91
Glycated albumin	1.0 [Ref]	1.25 (0.35–4.50)	0.59 (0.15–2.33)	1.00 (0.17–6.00)	0.86
1,5-AG	1.0 [Ref]	0.58 (0.15–2.28)	1.10 (0.31–3.90)	0.53 (0.15–1.89)	0.57
100–125 mg/dL (N = 661)†					
Fructosamine	1.0 [Ref]	0.73 (0.23–2.34)	2.41 (1.07–5.47)	1.97 (0.81–4.80)	0.03
Glycated albumin	1.0 [Ref]	1.00 (0.33–3.03)	1.72 (0.64–4.67)	3.15 (1.24–8.01)	0.01
1,5-AG	1.0 [Ref]	0.81 (0.34–1.90)	1.28 (0.58–2.81)	0.32 (0.12–0.90)	0.06
Hemoglobin A_{1c}					
<5.7% (N = 880)†					
Fructosamine	1.0 [Ref]	1.37 (0.49–3.79)	2.74 (1.14–6.62)	1.42 (0.47–4.31)	0.19
Glycated albumin	1.0 [Ref]	1.07 (0.41–2.80)	1.54 (0.62–3.83)	2.14 (0.76–5.99)	0.13
1,5-AG	1.0 [Ref]	0.43 (0.17–1.11)	1.36 (0.59–3.16)	0.38 (0.14–1.08)	0.27
5.7–6.4% (N = 359)†					
Fructosamine	1.0 [Ref]	1.26 (0.20–7.94)	4.55 (1.16–17.83)	10.56 (2.69–41.39)	<0.001
Glycated albumin	1.0 [Ref]	1.08 (0.18–6.61)	3.61 (1.09–11.94)	8.56 (2.61–28.09)	<0.001
1,5-AG	1.0 [Ref]	1.22 (0.42–3.49)	1.43 (0.47–4.39)	0.36 (0.10–1.32)	0.14

All models were adjusted for age, sex, race, total cholesterol, HDL cholesterol, BMI, average systolic blood pressure, family history of diabetes, and smoking status. *P value for trend evaluated using an ordinal variable based on the median value in each quartile. †N represents the unweighted number in each strata.

setting in which alternative markers eventually could be used, our main analysis focused on associations in a community-based population of persons with no history of diagnosed diabetes. Such an analysis also is directly relevant to other epidemiologic studies in which fasting glucose and A1C measurements are not available and in which alternative markers of glycemic control might have utility. However, a number of participants had undiagnosed diabetes at baseline, i.e., a baseline A1C $\geq$6.5% (N = 60) or a baseline fasting glucose $\geq$126 mg/dL (N = 77). In sensitivity analyses, we observed significant associations for fructosamine and glycated albumin, but not for 1,5-AG, with incident diagnosed diabetes among participants with a fasting glucose of 100 to 125 mg/dL or an A1C of 5.7–6.4%.

It is striking that both fructosamine and glycated albumin provided additional prognostic information regarding diabetes risk above and beyond baseline A1C. This may partially reflect weaknesses of A1C, particularly in the nondiabetic range, in which nonglycemic factors such as hemoglobin glycation or erythrocyte characteristics may have disproportionate influence (20). It also may reflect the inherent variability in any single measure of a blood analyte (21,22). The within-person variability in single measures of A1C and fasting glucose are such that adding an additional marker may improve identification of persons at risk for diabetes (23).

1,5-AG is a serum monosaccharide with a half-life of ~1 to 3 days (2,24). In a nondiabetic person, ~5 to 10 mg/mL of 1,5-AG are filtered daily through the glomeruli and reabsorbed by the proximal tubule (2). In the setting of acute hyperglycemia, glucose spills into the urine and competes with 1,5-AG reabsorption, which results in increased excretion of 1,5-AG and lower serum concentrations (2). Because of its inverse association with hyperglycemia, 1,5-AG is generally thought to have utility as an intermediate marker of glycemic control (25) or to monitor postprandial hyperglycemia (8,9). 1,5-AG is approved by the Food and Drug Administration for monitoring short-term glycemic control in persons with diabetes and is sometimes used for monitoring postprandial hyperglycemia (8,9). Although previous research has shown 1,5-AG to be related to changes in hyperglycemia (25), our study represents the first demonstration of a

significant association between 1,5-AG and the subsequent development of diabetes. However, consistent with its physiologic handling, 1,5-AG was not significantly associated with incident diabetes among persons with a fasting glucose <126 mg/dL or A1C <6.5%, suggesting limited utility for 1,5-AG in the setting of normal glucose and A1C levels.

Our study has several limitations. The maximum length of follow-up was 5.7 years and only 119 new cases of diagnosed diabetes occurred in this community-based population of 1,299 persons without a history of diagnosed diabetes at baseline. Correspondingly, the precision of some of our estimates was low, as indicated by the wide confidence intervals. Because of sample size limitations, we were unable to examine the consistency of the observed associations across subgroups of the population. We had only single measurements of each of the glycemic markers at baseline and no follow-up measurements of A1C or fasting glucose to identify incident cases of undiagnosed diabetes. Although self-report of diagnosed diabetes has been previously validated and shown to be highly specific for the identification of cases of diabetes in the ARIC study population (16), this case definition underestimates risk factor associations as compared with definitions that incorporate glucose criteria (15). Finally, abnormal glucose test results were provided to participants and their physicians (if desired), which could account for the more robust association between baseline fasting glucose and future diagnosis of diabetes as compared with the other biomarkers (results of which were not provided to participants) (26). Strengths of this study include the rigorous measurement of diabetes risk factors, the relatively large biethnic community-based sample, the comparative analyses of different glycemic markers, and excellent laboratory performance demonstrated for all measures of hyperglycemia examined here.

In conclusion, we found that fructosamine, glycated albumin, and 1,5-AG were strongly associated with diabetes risk. Our results suggest that elevations in these measures of short-term hyperglycemia may be useful indicators of a future diabetes risk, independently of single baseline fasting glucose and A_{1c} measurements in persons without a previous diagnosis of diabetes. Additional studies are needed to investigate the associations of these alternative markers of

glycemic control and long-term complications of diabetes and their potential clinical utility for monitoring glycemic control.

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