Serum Fructosamine and Glycated Albumin and Risk of Mortality and Clinical Outcomes in Hemodialysis Patients

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OBJECTIVE—Assays for serum total glycated proteins (fructosamine) and the more specific glycated albumin may be useful indicators of hyperglycemia in dialysis patients, either as substitutes or adjuncts to standard markers such as hemoglobin A_{1c}, as they are not affected by erythrocyte turnover. However, their relationship with long-term outcomes in dialysis patients is not well described.

RESEARCH DESIGN AND METHODS—We measured fructosamine and glycated albumin in baseline samples from 503 incident hemodialysis participants of a national prospective cohort study, with enrollment from 1995–1998 and median follow-up of 3.5 years. Outcomes were all-cause and cardiovascular disease (CVD) mortality and morbidity (first CVD event and first sepsis hospitalization) analyzed using Cox regression adjusted for demographic and clinical characteristics, and comorbidities.

RESULTS—Mean age was 58 years, 64% were white, 54% were male, and 57% had diabetes. There were 354 deaths (159 from CVD), 302 CVD events, and 118 sepsis hospitalizations over follow-up. Both fructosamine and glycated albumin were associated with all-cause mortality; adjusted HR per doubling of the biomarker was 1.96 (95% CI 1.38–2.79) for fructosamine and 1.40 (1.09–1.80) for glycated albumin. Both markers were also associated with CVD mortality [fructosamine 2.13 (1.28–3.54); glycated albumin 1.55 (1.09–2.21)]. Higher values of both markers were associated with trends toward a higher risk of hospitalization with sepsis [fructosamine 1.75 (1.01–3.02); glycated albumin 1.39 (0.94–2.06)].

CONCLUSIONS—Serum fructosamine and glycated albumin are risk factors for mortality and morbidity in hemodialysis patients.

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Diabetes is the leading cause of end-stage renal disease (ESRD), and patients with diabetes on dialysis have poor survival with a 5-year cumulative mortality >70% (1). The interplay between glucose homeostasis and advanced kidney failure is complex. Although there is increasing insulin resistance in advanced kidney failure, a concomitant decrease in insulin metabolism by the kidney and poor appetite caused by uremia often lead to euglycemia and discontinuation of hypoglycemic medications in patients with diabetes in the pre-ESRD period. The initiation of dialysis is often followed by an improvement of appetite and caloric intake and may lead to worsening of hyperglycemia and its associated complications. However, in dialysis patients, the optimal method to assess hyperglycemia remains a matter of debate (2).

Hemoglobin A_{1c} (HbA_{1c}) is the standard measure used to monitor glycemic control in clinical practice. HbA_{1c} measures the percent of hemoglobin in circulating erythrocytes that has chemically reacted with glucose and represents the average glycemia over the prior 2–3 months. In dialysis patients, shortened erythrocyte survival may lead to the underestimation of hyperglycemia based on the HbA_{1c} measurement (3,4). Plasma proteins also undergo glycation and might be unaffected by factors that influence red cell turnover. Serum fructosamine measures all serum proteins that undergo glycation, whereas serum glycated albumin specifically measures albumin that has undergone glycation. Both fructosamine and glycated albumin represent short-term (1–3-week) glycemia (5,6). Although a number of previous studies have reported the association between HbA_{1c} and outcomes in dialysis patients (7,8), the relationship of serum glycated proteins to clinical outcomes has not been well characterized.

The aim of this study was to examine the association of fructosamine and glycated albumin with morbidity and mortality in dialysis patients. We measured fructosamine and glycated albumin in stored serum samples from the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) study, a prospective cohort study of incident dialysis patients. We were unable to obtain HbA_{1c} measurements in all participants at baseline, but HbA_{1c} data were available in a subset of participants with diagnosed diabetes as part of routine clinical testing.

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RESEARCH DESIGN AND METHODS

Study design

The CHOICE study is a national prospective cohort of incident dialysis patients (9). From October 1995 to June 1998, 1,041 participants (767 on hemodialysis) from 19 U.S. states were enrolled a median of 45 days after initiation of dialysis (95% within 3.5 months). Follow-up for all-cause mortality was available through 31 December 2008 and for cardiovascular disease (CVD) mortality through 31 December 2004. Eligibility criteria were new onset of long-term dialysis therapy in the preceding 3 months, ability to provide informed consent, >18 years of age, and ability to speak English or Spanish. A specimen bank was established among the Dialysis Clinics, Inc. (DCI) participants of the CHOICE study. Nonfasting, predialysis blood specimens were centrifuged within 30–45 min of blood collection and sent overnight on ice to the DCI central laboratory. Each blood collection was aliquoted into multiple vials and stored at −80°C. The current study included 503 hemodialysis participants with banked sera. Among these participants, the median time from dialysis initiation to blood collection was 4.8 months (25th–75th percentile, 3.8–6.1 months). Hemodialysis patients with available sera were younger on average (58 vs. 62 years of age), had a higher average diastolic blood pressure (80 vs. 77 mmHg), were less likely to be white (64 vs. 76%), and were more likely to have completed at least some college (34 vs. 26%), compared with those without stored sera. The Johns Hopkins Medicine institutional review board and the clinical centers' review boards approved the study, and participants provided written informed consent.

Measurement of fructosamine and glycated albumin

Serum fructosamine was measured by a colorimetric nitroblue tetrazolium assay, and total serum albumin and glycated albumin were measured using an enzymatic/colorimetric assay (Asahi Kasei Pharma Corporation, Tokyo, Japan). Both assays were implemented on a Roche Modular P800 Chemistry Analyzer (Roche Diagnostics, Indianapolis, IN) at the University of Minnesota. The coefficient of variation (CV) for fructosamine was 3.2% at 221 μmol/L and 2.6% at 702 μmol/L. The reliability coefficient for fructosamine in a 5% sample of masked duplicate specimens assayed on different days was 0.957. As per the manufacturer's instructions, the glycated albumin (%) was computed as [(glycated albumin in g/dL/serum albumin in g/dL)*100/1.14] + 2.9. The CV for glycated albumin was 2.2% at 0.56 g/dL and 1.3% at 1.64 g/dL. The reliability coefficient for glycated albumin in masked duplicate specimens was 0.998. Serum albumin was measured in the same specimen as glycated albumin and fructosamine at the University of Minnesota using bromocresol purple (CV 1.9%).

Outcome assessment

All-cause and CVD mortality were independently adjudicated using information from the clinic report, hospital records, National Death Index, Centers for Medicare and Medicaid Services death notification forms, and Social Security records, as previously described (10). The first CVD event (fatal or nonfatal) during follow-up was defined as an event due to myocardial infarction, cardiac revascularization procedure, stroke, carotid endarterectomy, extremity gangrene or peripheral revascularization procedure, limb amputation, or abdominal aortic aneurysm repair (10). Hospitalizations with sepsis were identified using the U.S. Renal Data System hospital billing claims with the ICD-9 codes 038.x (septicemia) or 790.7 (bacteremia).

Diabetes, comorbidities, and other variables

Participants self-reported age, sex, race, work history, and medical history, including diabetes and predialysis care. BMI [calculated as weight (kg)/(height in meters)^2] was calculated based on the height and weight reported on the 2728 form. Baseline comorbidities, including diabetes and prevalent CVD, were independently adjudicated by abstraction of dialysis unit records, hospital discharge summaries, medication lists, consultation notes, diagnostic imaging, and cardiac imaging reports and scoring of the Index of Coexistent Disease (ICED) by two trained nurses. Comorbidities were scored using the ICED, a validated medical record–derived index that captures both presence and severity of comorbid conditions (11,12). ICED scores range from 0 to 3, with 3 as the highest severity level. Data on the use of medications at baseline were abstracted from patient charts.

Laboratory data from routine patient care were available for serum calcium, phosphorus, potassium, glucose, hemoglobin, and HbA_{1c}. HbA_{1c} was measured at the central DCI laboratory (Nashville, TN) using high-performance liquid chromatography. Glucose was measured using the hexokinase method. HbA_{1c} was available for 117 (41%) study participants with diagnosed diabetes. Of these participants, 82% (96 of 117) had HbA_{1c} measurements from the same date as the collection of the blood samples used for fructosamine and glycated albumin; the rest were from within a 90-day window. High-sensitivity C-reactive protein was measured using a colorimetric competitive enzyme-linked immunosorbent assay (CV 8.9%), as previously described (13).

Statistical analysis

Baseline characteristics of participants were compared across categories of fructosamine and glycated albumin. Relationships between fructosamine and glycated albumin with random serum glucose and HbA_{1c} were compared using scatterplots and Pearson and Spearman correlation coefficients. Missing data for variables were as follows: educational status (2.8%), smoking history (2.8%), BMI (5.6%), and systolic blood pressure (3.8%). Missing data values were imputed with 10 data replicates using multiple imputation by the chained equations method implemented by the ice program in Stata. Cox proportional hazards models were used to investigate the associations between baseline fructosamine and glycated albumin and risk of mortality, first CVD event, or first sepsis hospitalization. Individuals were censored at transplantation or at the end of the study period. Proportional hazards assumptions were checked graphically and by hypothesis-based tests ($P > 0.05$). The linearity of continuous variables was assessed graphically by plots of martingale residuals and by likelihood ratio tests (14). Natural log transformations of both fructosamine and glycated albumin provided the best model fit. Given the evidence for nonlinearity, we also categorized fructosamine and glycated albumin into quintiles (fifths) at baseline. We further divided the highest quintile into two categories at the median for that quintile. Hazard ratios (HRs) were used to quantify the associations with fructosamine and glycated albumin for each outcome after adjustment for a priori defined confounders, including demographic

characteristics [age, sex, race (white or other), and educational status (completed high school or not)] and clinical and treatment factors [smoking history (ever smoked), systolic blood pressure (4th order polynomial transformation), BMI (natural log transformation), ICED score (0–3), CVD, albumin (natural log transformation), hemoglobin, total cholesterol, and C-reactive protein (natural log transformation)]. Graphical displays of HR were constructed with markers modeled as restricted cubic splines with the 10th percentile of the marker as the reference point. We performed sensitivity analyses to determine the robustness of our findings within subgroups with clinically measured HbA_{1c} or treated diabetes, and among those with clinically measured total serum protein. Statistical analyses were performed using Stata software, version 11.1 (Stata Corp.). Statistical significance was defined as $P < 0.05$ using two-tailed tests.

RESULTS

Baseline characteristics

Baseline characteristics of the participants by categories of fructosamine and glycated albumin are presented in Tables 1 and 2. Higher categories of both markers were associated with greater comorbidity, including CVD and diabetes as well as higher systolic blood pressure, potassium, and alkaline phosphatase. Higher fructosamine was associated with higher total protein and albumin, whereas higher glycated albumin was associated with lower albumin. Both fructosamine and glycated albumin were moderately correlated with random serum glucose among all participants (Spearman correlations of 0.562 and 0.688, respectively) and among those with diagnosed diabetes (Spearman correlations of 0.487 and 0.590, respectively) (see also Supplementary Figs. 1 and 2).

All-cause and CVD mortality

Of the 503 participants at baseline, 354 died during 1,860 person-years of follow-up (median 3.5 years). Both fructosamine and glycated albumin were associated with all-cause mortality in the overall model, and there was no statistical interaction between the markers and diabetes status on the risk of outcomes (Table 3). Among people with diagnosed diabetes, fructosamine and glycated albumin were both associated with all-cause mortality, although the association of glycated albumin was of borderline statistical significance ($P = 0.06$). To explore a possible nonlinear association between fructosamine and glycated albumin and mortality, we used restricted cubic splines to model the adjusted HR (Fig. 1*A* and *B*) and also calculated the HRs across categories of fructosamine and glycated albumin (Supplementary Tables 1 and 2). For fructosamine, there was a linear increase in the HR with increasing values of fructosamine below the median (302 μmol/L). In spline models, the HR for death per SD increase in fructosamine was 1.92 (95% CI 1.24–3.00; $P = 0.004$) below the median and 1.12 (0.95–1.31; $P = 0.18$) above the median (P value for change in slope = 0.04). Similar trends were seen in the categorical analysis (Supplementary Tables 1 and 2). For glycated albumin, the increase in HR was linear and there was no difference in the association below or above the median ($P = 0.90$).

There were 159 deaths due to CVD, with the specific causes as follows: coronary artery disease, 120 (75.5%); stroke, 23 (14.5%); peripheral arterial disease, 10 (6.3%); and ischemic bowel, 6 (3.8%). Both fructosamine and glycated albumin were associated with the risk of CVD death (Table 3 and Fig. 1*C* and *D*). In spline models, the HR for CVD death per SD increase in fructosamine was 2.83 (95% CI 1.44–5.57; $P = 0.003$) below the median (302 μmol/L) and 1.06 (95% CI 0.85–1.32; $P = 0.63$) above the median (P value for change in slope = 0.01). Glycated albumin was associated with a linear increase in risk (P for change in slope = 0.47).

CVD events and sepsis hospitalizations

There were 302 CVD events (Table 3). Both fructosamine and glycated albumin were associated with an increased risk of CVD events, and there was evidence for a nonlinear association of fructosamine with CVD events (Fig. 1*E* and *F*). The HR for CVD death per SD increase in fructosamine was 2.37 (95% CI 1.46–3.85; $P = 0.001$) below the median (302 μmol/L) and 1.14 (0.97–1.34; $P = 0.11$) above the median (P value for change in slope = 0.01). Glycated albumin was associated with a linear increase in risk (P for change in slope at the median = 0.95).

There were 118 hospitalizations with sepsis. Both fructosamine and glycated albumin were associated with sepsis hospitalizations (Table 3). The nonlinear pattern with fructosamine was also noticeable with sepsis hospitalizations (Fig. 1*G* and *H*), although the results from the spline model were not statistically significant.

Subgroup analyses

HbA_{1c} values were available for 117 (41%) of participants with diagnosed diabetes. Those with available HbA_{1c} were younger (4.7 years; $P = 0.001$), less likely to have CVD (62 vs. 74%; $P = 0.03$), and more likely to be on insulin (67 vs. 54%; $P = 0.03$) compared with diabetic participants without available HbA_{1c} values. Supplementary Table 3 shows the baseline characteristics of this subgroup of the population according to tertiles of HbA_{1c} at baseline. In this subgroup, fructosamine and glycated albumin were moderately correlated with clinically measured HbA_{1c} with Spearman correlations of 0.62 and 0.74, respectively (Supplementary Fig. 1*C* and *D*). In the subgroup with available HbA_{1c}, the direction and magnitude of association of mortality with fructosamine and glycated albumin were similar to the primary analysis of people with diagnosed diabetes. The adjusted HR for all-cause mortality per doubling of HbA_{1c} was 2.30 (95% CI 0.71–7.41; $P = 0.16$). The adjusted HR for all-cause mortality per doubling of fructosamine was 2.73 (1.06–7.03; $P = 0.04$) and for glycated albumin was 2.53 (1.13–4.50; $P = 0.02$). Similar nonsignificant trends were observed for HbA_{1c} for other outcomes (Supplementary Table 4).

There were 170 (59%) participants with diabetes being treated with insulin or oral hypoglycemic agents at baseline and, of these, 78 had available HbA_{1c} values (mean 7.3%, SD 1.7%). In this subgroup, the adjusted HRs for all-cause mortality per doubling of biomarker were as follows: HbA_{1c}, 1.19 (95% CI 0.23–6.20; $P = 0.84$); fructosamine, 1.70 (0.78–3.68; $P = 0.18$); and glycated albumin, 1.45 (0.84–2.50; $P = 0.18$). Although these results were not statistically significant, the magnitude and direction of effect was similar to the primary analysis.

We also analyzed the effect of adjustment for serum albumin or total serum protein concentration on the association of fructosamine and glycated albumin with mortality. As might be expected, since the expression of glycated albumin is a ratio of glycated albumin to total serum albumin, there was a greater influence of adjustment for serum albumin or total protein on fructosamine than on glycated albumin. After adjustment for all

Table 1—*Baseline characteristics of 503 incident hemodialysis participants of the CHOICE study by fructosamine categories*

		Serum fructosamine (range, μmol/L)					
	n	Quintile 1 (143–255)	Quintile 2 (256–289)	Quintile 3 (290–318)	Quintile 4 (319–381)	Quintile 5.1 (383–430)	Quintile 5.2 (432–755)
Number		103	100	100	102	49	49
Markers of glycemia							
Random glucose (mg/dL)	500						
Mean (SD)		121 (38)	127 (36)	150 (70)	184 (76)	224 (87)	287 (163)
Median (25th–75th percentile)		114 (93–134)	117 (101–147)	130 (98–186)	166 (123–229)	211 (161–266)	240 (188–318)
HbA_{1c} (%)	117						
Mean (SD)		5.8 (1.4)	6.0 (1.1)	6.3 (1.2)	7.0 (1.2)	7.2 (0.8)	9.0 (1.7)
Median (25th–75th percentile)		5.4 (4.9–6.0)	5.7 (5.1–6.5)	5.6 (5.4–7.1)	7.3 (6.7–7.9)	7.3 (6.6–7.9)	9.0 (7.7–9.9)
Fructosamine (μmol/L)	503						
Mean (SD)		228 (25)	273 (9)	302 (8)	350 (19)	402 (12)	518 (79)
Median (25th–75th percentile)		234 (215–248)	271 (266–281)	302 (295–309)	349 (332–367)	402 (393–411)	501 (460–539)
Glycated albumin (%)	503						
Mean (SD)		13.3 (2.1)	15.2 (2.7)	17.3 (4.3)	20.4 (5.3)	26.6 (4.7)	38.0 (10.9)
Median (25th–75th percentile)		13.3 (12.0–14.6)	14.6 (13.2–16.1)	16.3 (14.3–19.6)	19.6 (16.7–24.2)	27.6 (23.9–29.4)	35.4 (29.6–46.9)
Demographic							
Age (years)	503	55 (16)	57 (15)	59 (15)	62 (12)	59 (13)	54 (13)
Sex (% female)	503	51	54	42	40	43	41
Race (% white)	503	66	68	64	62	59	59
Education (% high school graduate)	489	56	71	68	70	58	71
Clinical							
Smoking status (% ever smoker)	489	62	54	63	55	60	60
Index of coexistent disease score (%)	502						
≤1		38	34	33	20	23	25
2		41	35	40	53	39	33
3		21	31	27	28	39	43
Diabetes (%)	503	20	32	60	78	98	96
CVD (%)	502	36	50	58	67	69	65
BMI (kg/m^2)	475	28 (9)	27 (6)	28 (7)	28 (7)	27 (7)	26 (6)
Systolic blood pressure (mmHg)	484	148 (18)	147 (17)	155 (17)	152 (16)	156 (17)	156 (22)
Diastolic blood pressure (mmHg)	484	81 (11)	78 (10)	81 (9)	78 (9)	79 (10)	81 (11)

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Table 1—*Continued*

	n	Serum fructosamine (range, μmol/L)					
		Quintile 1 (143–255)	Quintile 2 (256–289)	Quintile 3 (290–318)	Quintile 4 (319–381)	Quintile 5.1 (383–430)	Quintile 5.2 (432–755)
ESRD related							
Assigned primary cause of renal failure (%)	503						
Diabetes	248	17	26	50	66	94	86
Hypertension	86	18	25	25	14	0	4
Glomerulonephritis	74	25	20	16	11	0	2
Average Kt/V	400	1.32 (0.31)	1.43 (0.29)	1.33 (0.28)	1.33 (0.25)	1.39 (0.23)	1.34 (0.22)
Average dialysis duration (min)	434	216 (25)	219 (23)	216 (21)	220 (23)	216 (21)	218 (25)
Laboratory							
Predialysis BUN (mg/dL)	404	55 (15)	58 (15)	61 (14)	60 (16)	57 (14)	62 (13)
Predialysis creatinine (mg/dL)	501	7.6 (2.5)	8.5 (2.8)	8.8 (3.3)	8.2 (3.0)	7.6 (2.1)	7.9 (2.6)
Potassium (mEq/L)	500	4.5 (0.6)	4.6 (0.6)	4.8 (0.7)	4.9 (0.6)	4.8 (0.5)	4.8 (0.6)
Total protein (g/dL)	456	6.7 (0.7)	6.8 (0.5)	6.9 (0.6)	7.0 (0.7)	7.0 (0.8)	7.0 (0.5)
Albumin (g/dL) (from glycated albumin measurement)	503	3.3 (0.6)	3.6 (0.5)	3.6 (0.5)	3.6 (0.6)	3.7 (0.6)	3.5 (0.5)
Calcium (mg/dL)	500	9.8 (0.9)	9.7 (0.8)	9.9 (0.9)	9.8 (0.8)	9.8 (0.7)	9.8 (0.9)
Phosphorus (mg/dL)	500	5.3 (1.4)	5.4 (1.4)	6.1 (1.7)	5.6 (1.7)	5.4 (1.5)	5.7 (1.4)
Hemoglobin (g/dL)	500	10.8 (1.3)	11.2 (1.1)	11.1 (1.2)	11.0 (1.0)	11.0 (1.0)	11.1 (1.1)
C-reactive protein (mg/dL); median (25th–75th percentile)	502	0.94 (0.39–2.19)	0.51 (0.18–1.15)	0.59 (0.28–1.35)	0.55 (0.25–1.54)	0.41 (0.28–1.12)	0.68 (0.40–1.24)
Others							
Total bilirubin (mg/dL)	457	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)	0.6 (0.2)	0.5 (0.1)	0.5 (0.1)
AST (units/L)	457	28 (10)	29 (16)	29 (10)	28 (11)	30 (15)	29 (10)
ALT (units/L)	457	21 (9)	21 (13)	21 (10)	22 (12)	25 (18)	25 (12)
Alkaline phosphatase (units/L)	457	92 (50)	89 (45)	98 (67)	99 (41)	127 (74)	125 (61)
Total cholesterol (mg/dL)	501	193 (53)	175 (32)	175 (32)	181 (44)	182 (40)	192 (43)
Baseline medications							
Any diabetes medication (%)	170	9	17	32	47	65	65
Insulin (%)	145	6	15	28	39	55	59
Oral hypoglycemic medications (%)	33	4	2	9	8	14	6
ACE inhibitors (%)	503	23	29	20	35	41	37
Calcium channel blockers (%)	503	51	55	67	70	69	61
β-Blockers (%)	503	35	25	24	18	20	20

Numbers presented are mean (SD) or percent unless otherwise specified. ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen. Conversion factors for units: glucose in mg/dL to mmol/L, ×0.05551; albumin in g/dL to g/L, ×10; calcium in mg/dL to mmol/L, ×0.2495; phosphorus in mg/dL to mmol/L, ×0.3229; hemoglobin in g/dL to g/L, ×10; BUN in mg/dL to urea in mmol/L, ×0.357; creatinine in mg/dL to μmol/L, ×88.4; bilirubin in mg/dL to μmol/L, ×17.1; cholesterol in mg/dL to mmol/L, ×0.02586. No conversion is necessary for potassium in mEq/L to mmol/L.

Table 2—*Baseline characteristics of 503 incident hemodialysis participants of the CHOICE study by glycated albumin categories*

		Serum glycated albumin (%)					
	n	Quintile 1 (7.6–13.4)	Quintile 2 (13.5–15.3)	Quintile 3 (15.4–18.6)	Quintile 4 (18.7–24.8)	Quintile 5.1 (25.5–30.1)	Quintile 5.2 (30.2–60.1)
Number		106	99	97	101	51	49
Markers of glycemia							
Random glucose (mg/dL)	500						
Mean (SD)		114 (33)	120 (32)	142 (53)	190 (63)	239 (80)	300 (165)
Median (25th–75th percentile)		109 (93–123)	117 (96–136)	129 (107–165)	185 (145–226)	232 (169–279)	240 (203–368)
HbA_{1c} (%)	117						
Mean (SD)		5.0 (0.2)	5.3 (0.6)	6.1 (1.0)	6.9 (1.0)	7.7 (1.0)	8.9 (1.7)
Median (25th–75th percentile)		5.1 (4.8–5.1)	2.0 (4.8–5.6)	6.0 (5.4–6.5)	6.7 (6.1–7.6)	7.4 (6.8–8.4)	8.8 (7.6–9.8)
Fructosamine (μmol/L)	503						
Mean (SD)		255 (42)	272 (42)	303 (41)	340 (52)	386 (51)	500 (96)
Median (25th–75th percentile)		253 (230–283)	271 (248–295)	298 (274–325)	335 (304–372)	395 (363–412)	499 (425–539)
Glycated albumin (%)	503						
Mean (SD)		12.2 (1.1)	14.4 (0.5)	16.5 (0.9)	21.4 (1.9)	28.0 (1.4)	40.0 (8.7)
Median (25th–75th percentile)		12.5 (11.9–13)	14.4 (13.9–14.7)	16.3 (15.7–17.1)	21.0 (19.7–22.7)	28.3 (26.8–29.3)	36.4 (32.6–46.9)
Demographic							
Age (years)	503	51 (16)	58 (16)	64 (13)	61 (12)	60 (12)	52 (13)
Sex (% female)	503	47	43	45	53	45	35
Race (% white)	503	67	67	59	69	61	53
Education (% high school graduate)	489	55	63	75	73	61	67
Clinical							
Smoking status (% ever smoker)	489	61	63	58	53	55	63
Index of coexistent disease score (%)	502						
≤1	149	46	33	24	27	16	20
2	206	35	44	53	34	45	35
3	147	19	22	24	40	39	45
Diabetes (%)	503	11	26	56	95	98	100
CVD (%)	502	30	52	60	73	67	65
BMI (kg/m^2)	475	28 (8)	26 (6)	27 (8)	29 (7)	27 (6)	25 (6)
Systolic blood pressure (mmHg)	484	148 (17)	147 (17)	151 (20)	157 (16)	154 (17)	158 (18)
Diastolic blood pressure (mmHg)	484	82 (10)	79 (10)	77 (10)	79 (9)	78 (10)	83 (9)

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Table 2—*Continued*

		Serum glycated albumin (%)					
	n	Quintile 1 (7.6–13.4)	Quintile 2 (13.5–15.3)	Quintile 3 (15.4–18.6)	Quintile 4 (18.7–24.8)	Quintile 5.1 (25.5–30.1)	Quintile 5.2 (30.2–60.1)
ESRD related							
Assigned primary cause of renal failure (%)	503						
Diabetes	248	8	18	44	83	48	47
Hypertension	86	22	30	23	8	1	2
Glomerulonephritis	74	35	20	15	2	2	0
Average Kt/V	400	1.33 (0.29)	1.39 (0.30)	1.36 (0.26)	1.35 (0.27)	1.37 (0.22)	1.34 (0.24)
Average dialysis duration (min)	434	214 (21)	217 (26)	219 (23)	218 (23)	218 (20)	220 (24)
Laboratory							
Predialysis BUN (mg/dL)	404	57 (15)	60 (16)	58 (15)	58 (14)	59 (15)	60 (12)
Predialysis creatinine (mg/dL)	501	8.7 (3.0)	8.9 (3.3)	8.4 (2.9)	7.3 (2.2)	7.5 (2.2)	7.4 (2.4)
Potassium (mEq/L)	500	4.6 (0.6)	4.7 (0.7)	4.8 (0.7)	4.7 (0.6)	4.8 (0.6)	4.7 (0.5)
Total protein (g/dL)	456	6.8 (0.6)	6.9 (0.7)	6.9 (0.6)	7.0 (0.7)	6.9 (0.7)	6.8 (0.6)
Albumin (g/dL)	503	3.7 (0.6)	3.6 (0.6)	3.6 (0.5)	3.5 (0.5)	3.4 (0.5)	3.3 (0.5)
Calcium (mg/dL)	500	9.8 (1.0)	9.7 (0.8)	9.8 (0.7)	9.9 (0.8)	9.8 (0.7)	9.8 (0.9)
Phosphorus (mg/dL)	500	5.6 (1.6)	5.8 (1.7)	5.5 (1.3)	5.4 (1.5)	5.6 (1.7)	5.5 (1.4)
Hemoglobin (g/dL)	500	11.1 (1.4)	11.1 (1.0)	10.9 (1.1)	11.0 (1.0)	11.0 (1.0)	11.0 (1.2)
C-reactive protein (mg/dL); median (25th–75th percentile)	502	0.61 (0.28–1.41)	0.50 (0.19–1.43)	0.61 (0.27–1.70)	0.69 (0.38–1.35)	0.63 (0.26–1.23)	0.63 (0.30–1.59)
Others							
Total bilirubin (mg/dL)	457	0.5 (0.1)	0.6 (0.1)	0.6 (0.2)	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)
AST (units/L)	457	28 (12)	28 (10)	31 (15)	27 (10)	31 (14)	28 (10)
ALT (units/L)	457	20 (9)	21 (10)	23 (14)	21 (10)	26 (19)	24 (10)
Alkaline phosphatase (units/L)	457	86 (37)	98 (62)	100 (69)	94 (32)	127 (73)	129 (61)
Total cholesterol (mg/dL)	501	186 (52)	178 (34)	178 (38)	183 (39)	178 (36)	193 (49)
Baseline medications							
Any diabetes medication (%)	170	4	11	29	57	67	71
Insulin (%)	145	2	10	24	49	59	63
Oral hypoglycemic medications (%)	33	2	3	6	12	12	8
ACE inhibitors (%)	503	20	30	28	28	33	51
Calcium channel blockers (%)	503	54	56	63	67	71	65
β-Blockers (%)	503	34	26	19	24	20	18

Numbers presented are mean (SD) or percent unless otherwise specified. ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen. Conversion factors for units: glucose in mg/dL to mmol/L, ×0.05551; albumin in g/dL to g/L, ×10; calcium in mg/dL to mmol/L, ×0.2495; phosphorus in mg/dL to mmol/L, ×0.3229; hemoglobin in g/dL to g/L, ×10; BUN in mg/dL to urea in mmol/L, ×0.357; creatinine in mg/dL to μmol/L, ×88.4; bilirubin in mg/dL to μmol/L, ×17.1; cholesterol in mg/dL to mmol/L, ×0.02586. No conversion is necessary for potassium in mEq/L to mmol/L.

Table 3—*Serum fructosamine and glycated albumin and outcomes in 503 participants of the CHOICE study*

			Crude model		Model 1**		Model 2***	
	Deaths	Total *n*	HR* (95% CI)	*P*	HR* (95% CI)	*P*	HR* (95% CI)	*P*
Fructosamine								
All-cause mortality								
All participants	354	503	1.64 (1.20–2.24)	0.002	1.61 (1.16–2.22)	0.004	1.96 (1.38–2.79)	<0.001
No diabetes	127	216	1.88 (0.73–3.70)	0.10	1.64 (0.73–3.70)	0.23	6.61 (2.01–21.8)	0.002
Diabetes	227	287	1.28 (0.83–1.95)	0.26	1.43 (0.92–2.24)	0.11	1.98 (1.18–3.30)	0.009
P interaction			0.28		0.79		0.25	
CVD mortality								
All participants	159	503	1.80 (1.14–2.82)	0.01	1.81 (1.12–2.92)	0.02	2.13 (1.28–3.54)	0.004
No diabetes	50	216	3.08 (0.85–11.2)	0.09	2.44 (0.60–10.0)	0.22	7.43 (1.06–52.91)	0.04
Diabetes	109	287	1.13 (0.62–2.06)	0.70	1.26 (0.67–2.38)	0.47	1.69 (0.82–3.48)	0.16
P interaction			0.09		0.27		0.17	
First CVD event								
All participants	302	503	1.85 (1.33–2.58)	<0.001	1.77 (1.24–2.50)	0.002	2.36 (1.64–3.42)	<0.001
No diabetes	94	216	1.84 (0.77–4.39)	0.17	1.26 (0.48–3.33)	0.64	3.0 (0.65–13.93)	0.16
Diabetes	208	287	1.16 (0.74–1.81)	0.53	1.26 (0.80–2.00)	0.32	1.72 (1.02–2.90)	0.04
P interaction			0.30		0.86		0.18	
First sepsis hospitalization								
All participants	118	503	1.66 (0.99–2.79)	0.06	1.61 (0.95–2.74)	0.08	1.75 (1.01–3.02)	0.05
No diabetes	37	216	0.90 (0.26–3.09)	0.86	0.70 (0.18–2.76)	0.60	****	
Diabetes	81	287	1.35 (0.67–2.73)	0.40	1.32 (0.64–2.71)	0.45	1.55 (0.71–3.38)	0.27
P interaction			0.75		0.60		0.96	
Glycated albumin								
All-cause mortality								
All participants	354	503	1.59 (1.28–1.98)	<0.001	1.60 (1.27–2.03)	<0.001	1.40 (1.09–1.80)	0.008
No diabetes	127	216	4.95 (1.91–12.86)	0.001	1.78 (0.62–4.90)	0.29	2.20 (0.73–6.69)	0.163
Diabetes	227	287	1.27 (0.93–1.73)	0.13	1.50 (1.08–2.08)	0.02	1.41 (0.98–2.01)	0.06
P interaction			0.004		0.71		0.56	
CVD mortality								
All participants	159	503	1.79 (1.32–2.43)	<0.001	1.85 (1.33–2.58)	<0.001	1.55 (1.09–2.21)	0.02
No diabetes	50	216	13.09 (3.38–50.70)	<0.001	2.61 (0.57–11.91)	0.22	2.75 (0.53–14.35)	0.23
Diabetes	109	287	1.24 (0.81–1.89)	0.32	1.45 (0.93–2.25)	0.11	1.23 (0.74–2.03)	0.43
P interaction			<0.001		0.14		0.14	
First CVD event								
All participants	302	503	1.79 (1.42–2.56)	<0.001	1.81 (1.41–2.33)	<0.001	1.66 (1.28–2.15)	<0.001
No diabetes	94	216	4.80 (1.62–14.21)	0.005	1.28 (0.33–3.91)	0.85	1.26 (0.29–5.39)	0.76
Diabetes	208	287	1.21 (1.87–1.67)	0.25	1.39 (0.99–1.94)	0.06	1.27 (0.88–1.83)	0.20
P interaction			0.01		0.86		0.73	
First sepsis hospitalization								
All participants	118	503	1.58 (1.10–2.26)	0.01	1.56 (1.08–2.25)	0.02	1.39 (0.94–2.06)	0.10
No diabetes	37	216	0.35 (0.08–1.60)	0.18	0.78 (0.03–1.08)	0.06	****	
Diabetes	81	287	1.42 (0.87–2.30)	0.16	1.42 (0.87–2.32)	0.16	1.28 (0.75–2.20)	0.36
P interaction			0.08	0.02			0.02	

*HR per doubling of the marker. Modeled as log(marker)/log(2). **Model 1, adjusted for demographic characteristics: age, race (white or other), sex, and educational status (completed high school or not). ***Model 2, adjusted for clinical and treatment factors in addition to demographic characteristics: smoking history (ever smoked), systolic blood pressure (4th order polynomial), BMI (log transformed), ICED score (0–3), CVD, hemoglobin, serum albumin (log transformed), total cholesterol, and C-reactive protein (log transformed). ****Model did not converge.

covariates except albumin, the HR per doubling of marker was 1.61 (95% CI 1.14–2.28) for fructosamine and 1.45 (1.14–1.86) for glycated albumin. After adjusting for serum albumin, the HR for fructosamine increased by 42% [1.96 (1.38–2.79)] compared with an 8% reduction in the HR for glycated albumin [1.40 (1.09–1.80)]. Similarly, after adjusting for total protein, the HR for fructosamine increased by 23% [1.81 (1.25–2.62)] compared with an 8% increase in the HR for glycated albumin [1.49 (1.15–1.92)].

CONCLUSIONS—In this report from a national prospective cohort study of incident hemodialysis patients, we found that serum fructosamine and glycated albumin were associated with an increased risk of all-cause mortality, CVD mortality, first CVD event, and first sepsis hospitalization, independent of rigorously measured potential confounding variables. There was some evidence for nonlinearity in the associations of fructosamine with mortality, with stronger

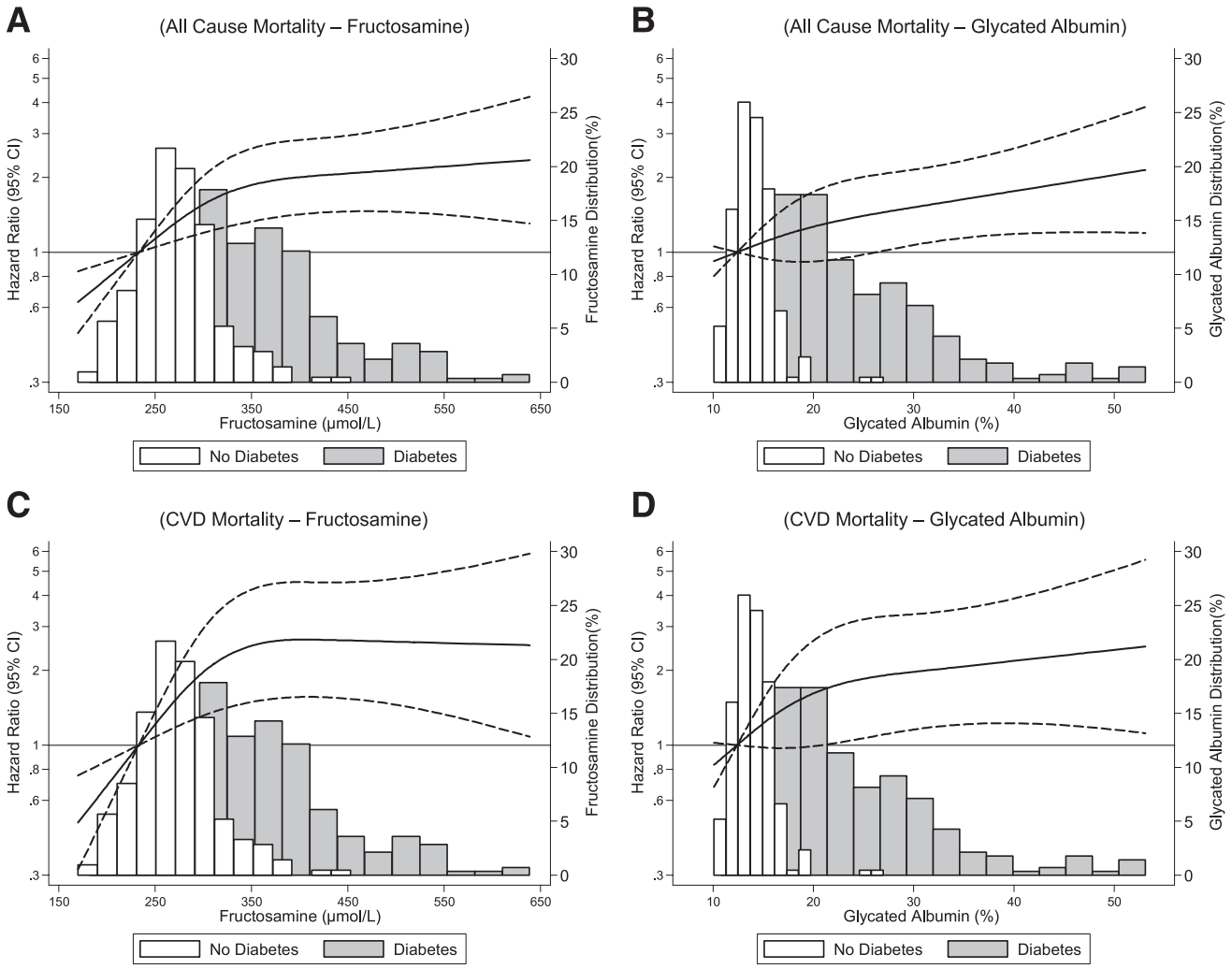

Figure 1—*Adjusted relative hazards of outcomes in 503 incident hemodialysis participants of the CHOICE study.* A *and* B*: Hazard of all-cause mortality with fructosamine and glycated albumin, respectively.* C *and* D*: Hazard of CVD mortality with fructosamine and glycated albumin, respectively.* E *and* F*: Hazard of first CVD event with fructosamine and glycated albumin, respectively.* G *and* H*: Hazard of first sepsis hospitalization with fructosamine and glycated albumin, respectively. Relative hazard predicted using Cox proportional hazards regression adjusted for demographic characteristics [age, race (white or other), sex, and educational status (completed high school or not)] and clinical and treatment factors [smoking history (ever smoked), systolic blood pressure, BMI, ICED score (0–3), CVD, albumin, hemoglobin, total cholesterol, and C-reactive protein]. Fructosamine and glycated albumin are modeled as restricted cubic splines with knots at the 10th, 50th, and 90th percentiles. The solid line is the adjusted HR of mortality; 10th percentile in the overall population was used as the reference (HR = 1). The dashed lines are the 95% CIs. Bars are the frequency histogram, showing the distribution of each serum marker; white bars represent those without diabetes and the gray bars represent those with diabetes.*

associations below the median (302 μmol/L). At values above the median, the association of fructosamine with mortality was relatively flat. This nonlinearity was also observed for CVD incidence and hospitalization risk. The glycated albumin associations were roughly linear for all outcomes.

Diabetes is the leading cause of ESRD in the U.S., and adjusted rates of incident ESRD due to diabetes, 154 per million population, are almost 1.5-fold higher than ESRD from hypertension and almost fivefold higher than ESRD from glomerulonephritis (1). The mortality of diabetic ESRD patients remains dismal, with <50% survival at 3 years, and CVD is the leading cause of death (1). Yet only 17% of the diabetic ESRD patients receive comprehensive, yearly diabetes monitoring including at least four HbA_{1c} tests, two lipid profiles, and one eye examination (1). Although therapeutic nihilism and inertia may be a contributing factor, skepticism remains about the role of aggressive glycemic control in controlling micro- and macrovascular complications of diabetes in a uremic milieu (2). In our study, HbA_{1c} measurements were only available in 41% of the participants with diagnosed diabetes, and among these participants, higher HbA_{1c} showed a trend toward increased mortality [HR 2.30 (95% CI 0.71–4.71)]. This association between HbA_{1c} and mortality mirrors previously reported findings from a large dialysis organization database (7,15,16). In contrast, a number of other studies have found no association between HbA_{1c} and mortality in diabetic dialysis patients (8,17,18). Although some of these conflicting findings may be the result of residual confounding and differences across study populations, they raise concerns about the prognostic value

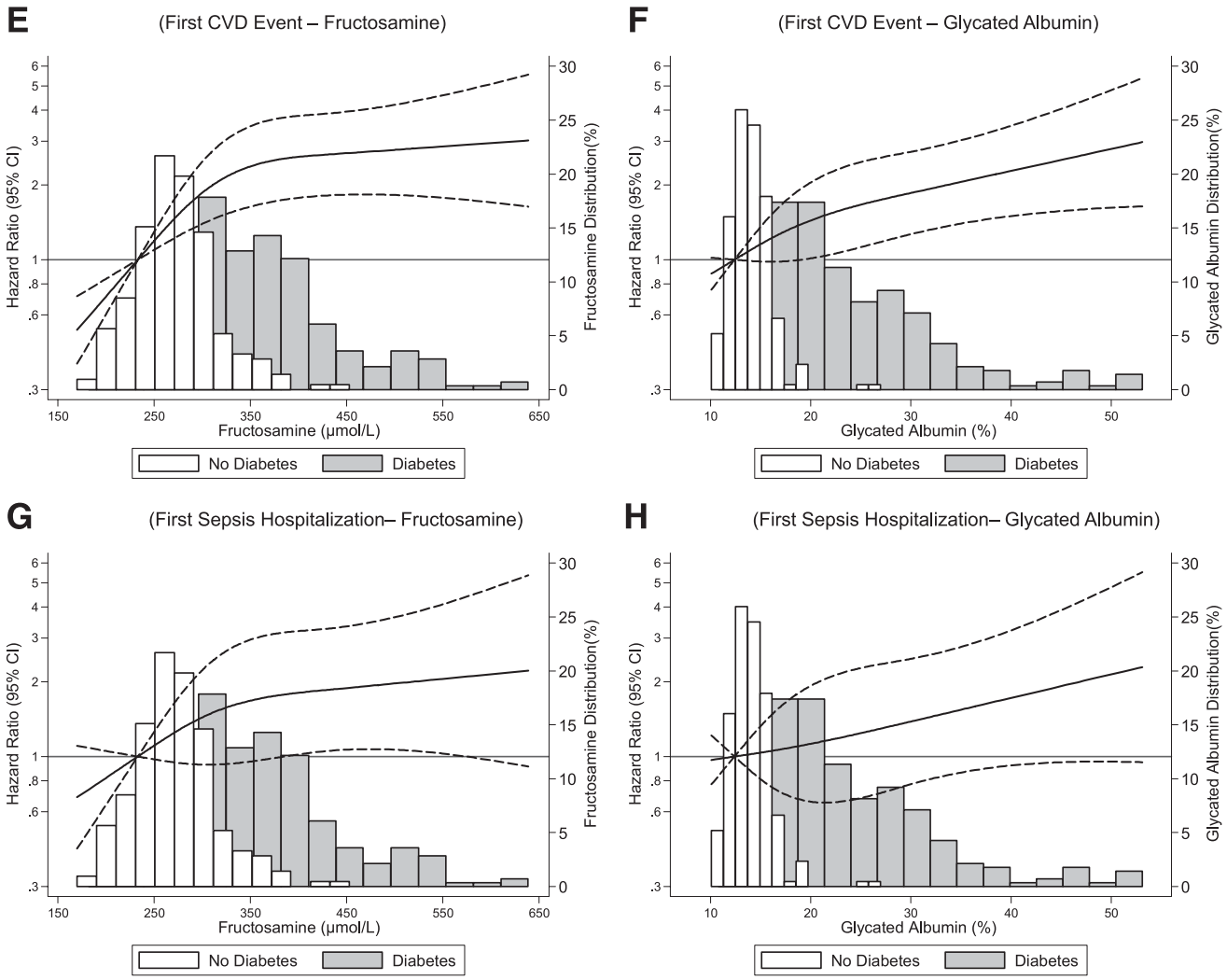

Figure 1—*Continued.*

of HbA_{1c} in dialysis patients, and the methods for assessment of glycemia in dialysis patients remains a subject of active debate (19,20).

HbA_{1c} is the mainstay for monitoring glycemia in patients with diabetes, but in previous studies of ESRD patients with diabetes, HbA_{1c} has been shown to significantly underestimate glycemia (3,4,21). This finding is likely the result of decreased erythrocyte survival in dialysis patients, as higher erythropoietin dose and lower hemoglobin values are associated with lower HbA_{1c} (4,22). Plasma proteins also undergo glycation and are unaffected by factors that influence red cell turnover. Fructosamine represents all serum glycated proteins that have stable ketoamines (carbonyl group of glucose reacting with an amino group of a protein) (5,6). Glycated albumin represents 90% of the glycated serum proteins (23). Glycated albumin, measured here using a novel enzymatic method, reflects the proportion of glycated albumin to total serum albumin (24). Although some prior studies suggest that glycated albumin is a better measure of glycemia in dialysis patients than HbA_{1c} (3,4,21,25), only one previous study has compared all three markers of glycemia in diabetic patients on hemodialysis (n = 31) and found that HbA_{1c} was the most correlated with predialysis serum glucose (26). Although serum proteins may not be affected by some of the factors that affect hemoglobin, such as iron stores and use of erythropoietin supplementation agents, increased albumin turnover can be seen in peritoneal dialysis patients and other dialysis patients with residual kidney function and significant proteinuria. Serum uric acid may also interfere with fructosamine measurements by nitroblue tetrazolium, leading to falsely higher fructosamine concentrations (23).

The association of serum fructosamine and mortality in dialysis patients has not been previously described, and, to our knowledge, only one study has reported the association between fructosamine and hospitalizations (27). Mittman et al. (27) measured serum fructosamine in 100 diabetic hemodialysis patients and found that it was associated with risk of infection and all-cause hospitalizations. Our study extends these findings, and we demonstrate an association of fructosamine with all-cause and CVD mortality as well as CVD events and sepsis hospitalizations.

The association between glycated albumin and outcomes in dialysis patients with diabetes has been previously evaluated in two single-center studies. Fukuoka et al. (28) analyzed the outcomes of 98 diabetic patients on hemodialysis

during 1992–2003 at Shigei Medical Research Hospital (Okayama, Japan). They found that glycated albumin was associated with all-cause mortality [HR per 1% increase, 1.04 (95% CI 1.01–1.07); P = 0.003] but not infectious or CVD death. HbA_{1c} was not significantly associated with mortality. Freedman et al. (17) recently reported the outcomes of 444 incident and prevalent dialysis patients (401 hemodialysis) treated at the Wake Forest University–affiliated dialysis units in North Carolina during January to June 2007. The updated mean of up to 6.09 glycated albumin measurements was associated with all-cause mortality [adjusted HR per 5% increase, 1.12 (0.99–1.27); P = 0.07] and hospitalization [HR per 5% increase, 1.02 (1.01–1.04)], whereas a single measurement of HbA_{1c} at baseline was not significantly associated with all-cause mortality or hospitalization risk in this population.

No prior studies have compared the associations of fructosamine and glycated albumin with long-term outcomes in a national dialysis cohort in the U.S. In our study, we found that both fructosamine and glycated albumin were similarly robust in predicting outcomes in dialysis patients with and without diabetes. This association between hyperglycemia and mortality in dialysis patients without diabetes has not been shown previously, but our results are generally consistent with the findings from studies of nondialysis populations (29,30).

In our study, higher fructosamine was associated with higher serum albumin and total protein levels, whereas higher glycated albumin was associated with lower serum albumin levels. Adjusting for albumin or total protein had a greater effect on the coefficient of fructosamine than glycated albumin. These results partially reflect the way serum fructosamine and glycated albumin are reported. Serum fructosamine represents the total glycated serum proteins, whereas glycated albumin is expressed as a ratio of glycated albumin to total albumin. As a result, the changes in serum protein concentration are likely to have a greater impact on serum fructosamine than glycated albumin.

Because of possible effect modification by diabetes status, we conducted analyses overall and stratified by a diagnosis of diabetes. However, as diabetes may be associated with macrovascular disease prior to ESRD, adjusting for diabetes may control for some residual confounding that may have existed in the overall model. Adjustment for diabetes (Supplementary Tables 1 and 2, model 3) attenuated the association between markers and outcomes, but the magnitude and direction of effect remain unchanged.

Our study has some limitations. First, stored samples were only available for 66% of the CHOICE hemodialysis cohort, which could have introduced a selection bias with inclusion of healthier participants compared with the full cohort. Second, HbA_{1c} measurements were only available in a subsample of participants with diagnosed diabetes. However, in analyses limited to the participants with HbA_{1c} data, the direction and magnitude of the associations of fructosamine and glycated albumin on mortality were similar to results in the total cohort, although power to detect associations in this subsample was limited due to the small sample size. Third, we only had single measurements of fructosamine and glycated albumin, which may be associated with significant within-person variability, particularly in a dialysis population. Fourth, the diagnosis of diabetes was based on self-report and available medical records and was not confirmed by oral glucose tolerance testing. As a result, individuals with undiagnosed diabetes were not classified as diabetes cases in this study. Finally, we only had information about diabetes medications at baseline and do not have information about the occurrence of hypoglycemia or discontinuation of therapy, which could have effects on outcomes. Nonetheless, this study has several strengths, including the prospective design, detailed information on demographic, clinical, and treatment factors, and systematic adjudication of baseline comorbid conditions as well as incident events. These comprehensive data allowed us to extensively adjust for numerous rigorously measured a priori defined potential confounders.

In summary, we found that both serum fructosamine and glycated albumin were risk factors for all-cause and CVD mortality, CVD events, and sepsis hospitalizations in hemodialysis patients. The measurement of these markers may be useful for the management of diabetes in dialysis patients.

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Asahi Kasei Pharma Corporation had no role in the design, analysis, and interpretation of data or the preparation of the manuscript.

T.S. researched data and wrote the manuscript. S.M.S., L.C.P., N.R.P., J.C., and E.S. contributed to the analysis and interpretation of the data. B.G.J., E.T.K., R.S.P., and M.W.S. reviewed and edited the manuscript and contributed to the interpretation and discussion. T.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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