Increases in Biomarkers of Hyperglycemia With Age in the Atherosclerosis Risk in Communities (ARIC) Study

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The American Diabetes Association's *Standards of Medical Care in Diabetes—2017* states that age should be "taken into consideration" when diagnosing diabetes with HbA_{1c} (1). Nonetheless, it is unclear how this recommendation might be implemented. Population studies demonstrate that HbA_{1c} increases with age, which some experts have suggested may be due to nonglycemic factors like alterations in red cell turnover or hemoglobin glycation (2–4). However, prior studies lack concurrent comparisons across nonhemoglobin-related markers of hyperglycemia. We evaluated increases with age in fructosamine and glycated albumin—hemoglobin-independent measures of hyperglycemia—in comparison with HbA_{1c} and fasting glucose in the community-based Atherosclerosis Risk in Communities (ARIC) study.

We conducted serial cross-sectional analyses at visit 2 (1990–1992; $n = 11,632$) and visit 5 (2011–2013; $n = 3,876$), excluding individuals with diagnosed diabetes. We performed adjusted linear regression of *z* scores of each biomarker (standardized to visit 2) on age to allow head-to-head comparisons of the associations.

Age was significantly correlated with all biomarkers of hyperglycemia at visit 2 (Fig. 1). In middle age (visit 2), we observed increases in HbA_{1c} with age, comparable increases in fructosamine and glycated albumin, and some increase in fasting glucose, with modest impact of adjustment for sex, race center (white, Minneapolis, MN; black, Jackson, MS; white, Washington County, MD; black, Forsyth County, NC; white, Forsyth County, NC; as defined by the ARIC study design), BMI, and BMI^2. At visit 5 among older adults (21 years later), increases with age were less evident for fasting glucose and HbA_{1c} compared with fructosamine and glycated albumin. Associations of age with HbA_{1c}, fructosamine, and glycated albumin at both visits persisted after further adjustment for fasting glucose.

The magnitude of the association we observed between HbA_{1c} and age, particularly in middle age (0.11% [1.2 mmol/mol] per 10 years of age), was similar to that in other studies (2–4). Prior investigations adjusted for glucose to account for glycemia and attributed associations to nonglycemic hemoglobin-related factors. However, although HbA_{1c} and fasting glucose are highly related, they represent different glycemic constructs. We observed increases in HbA_{1c}, fructosamine, and glycated albumin independent of fasting glucose, suggesting that increases may be primarily glycemic or that putative nonglycemic factors may influence nonhemoglobin biomarkers.

The heterogeneity of dysglycemia across the life span may offer some explanation for the less consistent associations of age across the hyperglycemia biomarkers. Impaired insulin secretion is common in older age. As HbA_{1c}, fructosamine, and glycated albumin reflect postprandial glucose excursions in addition to fasting concentrations, their stronger associations with age as compared with fasting glucose could reflect that impaired glucose tolerance is more common than impaired fasting glucose in this population (5).

Similar to previous investigations, our assessment is limited by its cross-sectional nature. Additionally, our analyses of older adults could be subject to selection bias. Study strengths include the community-based sample, broad age range, and measurements at different time points in the life span.

In conclusion, we observed higher HbA_{1c} at older ages but also saw comparable associations for other (nonhemoglobin-related) biomarkers of hyperglycemia. Our results provide some evidence that the age associations with HbA_{1c}, fasting glucose, fructosamine, and glycated albumin may reflect increases in the prevalence of hyperglycemia in aging.

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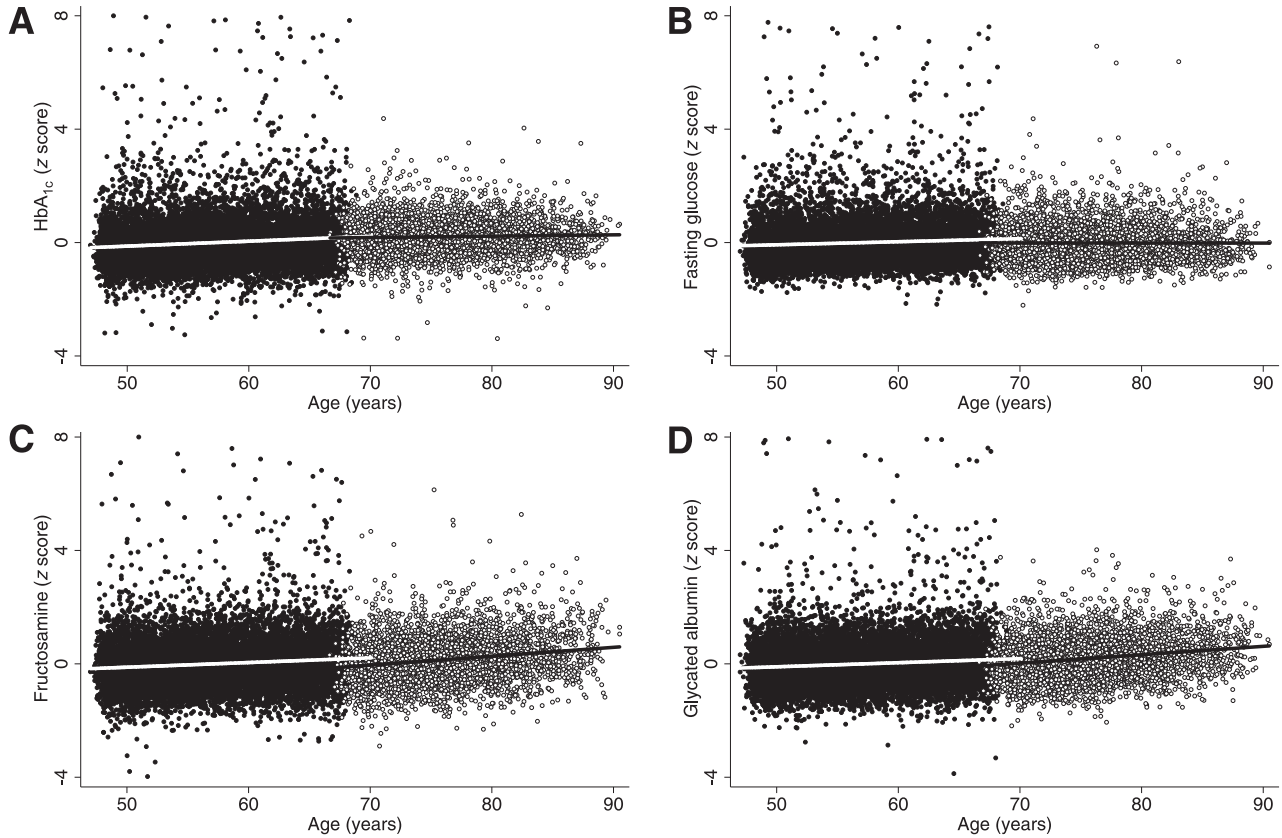

		VISIT 2 (1990-1992)		VISIT 5 (2011-2013)	
Panel	Biomarker	*r*	β_z, per 10 years (95% CI)	*r*	β_z, per 10 years (95% CI)
A	HbA_{1c}	0.099**	0.173 (0.142, 0.205)	0.038*	0.048 (0.009, 0.087)
B	Fasting glucose	0.062**	0.109 (0.077, 0.140)	-0.002	-0.002 (-0.045, 0.041)
C	Fructosamine	0.094**	0.165 (0.133, 0.197)	0.188**	0.315 (0.263, 0.366)
D	Glycated albumin	0.082**	0.144 (0.112, 0.176)	0.197**	0.297 (0.251, 0.344)

Figure 1—Scatterplots with linear predictions, Pearson correlation coefficients, and unadjusted β coefficients (95% CIs) from linear regressions of *z* scores of markers of hyperglycemia (standardized to visit 2) on age (visit 2: 1990–1992 and visit 5: 2011–2013). HbA_{1c} (*A*), fasting glucose (*B*), fructosamine (*C*), and glycated albumin (*D*). Black circles, visit 2 biomarker values; white line, visit 2 linear prediction; white circles, visit 5 biomarker values; black line, visit 5 linear prediction. *$P < 0.05$, **$P < 0.001$.

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