Letters to the Editor

Total Short-term Variability in Biomarkers of Hyperglycemia in Older Adults

To the Editor:

There is growing interest in the use of nontraditional short-term biomarkers of hyperglycemia [fructosamine, glycated albumin, and 1,5-anhydroglucitol (1,5-AG)][1] to complement fasting glucose and hemoglobin A_{1c} (Hb A_{1c}) for prognosis and management of diabetes (1). Within-person variability in Hb A_{1c} and fasting glucose has been previously characterized (2–4), but little is known about the variability of these alternative biomarkers of hyperglycemia in the general population. We quantified the 6-week total variability in fructosamine, glycated albumin, and 1,5-AG in older adults with and without diabetes and compared it to that of fasting glucose and Hb A_{1c}.

We included 153 participants from the Atherosclerosis Risk in Communities (ARIC) Study (5) who attended the initial visit-5 exam (2011–13), returned for a second visit scheduled 4–8 weeks later, had complete data, fasted ≥8 h at both visits, and did not have outlying values. Institutional review boards approved all procedures, and all study participants provided written informed consent.

Serum fructosamine, glycated albumin, and 1,5-AG were measured with the Roche Cobas 6000 (Roche Diagnostics). Fructosamine was measured with a colorimetric method (Roche Diagnostics). Glycated albumin (Asahi Kasei Lucica GA-L) and 1,5-AG (GlycoMark) were measured with enzymatic methods. Glucose was measured in plasma with an Olympus 480 analyzer (Beckman Coulter) and a hexokinase method. Hb A_{1c} was measured in whole blood with HPLC (Tosoh G7, Tosoh Medics) standardized to the Diabetes Control and Complications Trial assay. Interassay CVs were 3.2% for fructosamine at a mean concentration of 220.3 µmol/L, 4.4% for glycated albumin at 0.45 g/dL, 0.9% for 1,5-AG at 18.0 µg/mL, 2.7% for glucose at 121.7 mg/dL, and 1.9% for Hb A_{1c} at 5.36%.

Analyses were conducted separately in those with and without diagnosed diabetes. For each biomarker, we calculated means by diabetes status: the mean at the original exam, the mean at the second exam, and the mean difference (second minus original). To partition the total variance of the repeated measurements into the between-subject variance (σ_{BS}^2) and within-subject variance (σ_{WS}^2), we used linear mixed-effects models with each biomarker as the dependent variable and the participant as a random effect. We calculated the between-person CV (CV_G): $[(\sqrt{\sigma_{BS}^2})/\mu]*100$, where μ is the mean of all values (both original and second measurements). Similarly, we calculated the within-person CV (CV_W): $[(\sqrt{\sigma_{WS}^2})/\mu]*100$. The CV_W is a function of the within-person biological coefficient of variation (CV_I) and the analytical coefficient of variation (CV_A) (or each method's CV reported by the laboratory): $CV_W = \sqrt{CV_A^2 + CV_I^2}$. We then calculated the index of individuality: $(\sqrt{CV_A^2 + CV_I^2})/CV_G$ or equivalently, CV_W/CV_G. We also calculated the intraclass correlation coefficient (ICC): $\sigma_{BS}^2/(\sigma_{BS}^2 + \sigma_{WS}^2)$. All statistical analyses were conducted with Stata, version 13.0 (StataCorp).

The mean age was 76 years, 33% had a diagnosis of diabetes, 39% were male, and 74% were white. The mean time between the original and second examinations was 45 days (SD, 16 days) (range 23–102 days). Estimates of total CV_W for fructosamine, glycated albumin, and 1,5-AG were 3.4%, 2.7%, and 2.9%, respectively, in those without diabetes, and 3.7%, 3.8%, and 5.7% in those with diabetes (Table 1). CV_W values for fasting glucose and Hb A_{1c} were similar to those previously reported (Table 1) (2, 3). The point estimates for the CV_W values were greater in those with diagnosed diabetes—60% of whom reported taking glucose-lowering medication—compared to those without diagnosed diabetes, although the CIs for fructosamine and glycated albumin in those with and without diabetes overlapped. The results in individuals with diabetes may partially reflect the influence of diabetes management on glycemic variability. The CV_W values of fructosamine, glycated albumin, and 1,5-AG were between those of fasting glucose and Hb A_{1c}. Of the nontraditional biomarkers, the ICC was lowest for fructosamine and highest for 1,5-AG (Table 1). Patterns of Spearman rank correlation coefficients were similar to those of ICCs (Table 1). All biomarkers had a favorably low index of individuality, with 1,5-AG having the lowest (Table 1). Results for Hb A_{1c} and fasting glucose were similar to previously reported findings (2–4).

Estimates of total variability of these biomarkers were intermediate between fasting glucose and Hb A_{1c}, consistent with their biology (1). Notably, 1,5-AG had very high correlations and estimates of reliability, which may be partially attributed to the relatively wide range of values for this biomarker. All biomarkers of hyperglycemia had a low index of individuality, which suggests that changes in biomarker levels over time within an individual primarily reflect biological change. Limitations of our study include having only 2 measurements for each participant and the use of internal laboratory QC materials instead of duplicates to obtain the analytical CV.

In summary, we found that nontraditional biomarkers of hyperglycemia are consistent over approximately 6 weeks and have lower within-person variability than fasting glucose. These data should help inform the use of

[1] Nonstandard abbreviations: 1,5-AG, 1,5-anhydroglucitol; Hb A_{1c}, hemoglobin A_{1c}; ARIC, Atherosclerosis Risk in Communities; ICC, intraclass correlation coefficient.

Table 1. Total variability in biomarkers of hyperglycemia in older adults with and without diabetes, ARIC, 2011–13, n = 153.[a]

	Original exam	Second exam	Difference (second minus original)	CV_W (95% CI)[b]	ICC (95% CI)[b]	r (95% CI)	Index of individuality (95% CI)[b]
No diagnosed diabetes (n = 103)							
Fructosamine, μmol/L	241.5 (22.9)	239.4 (21.0)	−2.10 (11.3)	3.4 (2.9–3.8)	0.86 (0.83–0.89)	0.83 (0.76–0.88)	0.40 (0.34–0.46)
Glycated albumin, %	13.8 (1.5)	13.7 (1.7)	−0.04 (0.5)	2.7 (2.3–3.0)	0.95 (0.94–0.96)	0.91 (0.88–0.94)	0.24 (0.20–0.27)
1,5-AG, μg/mL	17.5 (6.0)	17.6 (6.1)	0.04 (0.7)	2.9 (2.7–3.2)	0.99 (0.99–0.99)	0.99 (0.99–0.99)	0.09 (0.08–0.09)
Fasting glucose, mg/dL	104.7 (17.6)	104.5 (15.9)	−0.18 (7.9)	5.3 (4.6–6.0)	0.89 (0.85–0.93)	0.72 (0.61–0.80)	0.35 (0.27–0.44)
Hb A_{1c}, %	5.7 (0.4)	5.7 (0.4)	−0.01 (0.1)	1.5 (1.3–1.7)	0.95 (0.95–0.96)	0.95 (0.92–0.96)	0.22 (0.19–0.25)
Diagnosed diabetes (n = 50)							
Fructosamine, μmol/L	263.2 (39.8)	261.8 (38.7)	−1.46 (13.6)	3.7 (3.0–4.3)	0.94 (0.92–0.96)	0.84 (0.73–0.90)	0.25 (0.20–0.31)
Glycated albumin, %	15.5 (2.8)	15.7 (2.9)	0.2 (0.8)	3.8 (2.9–4.7)	0.95 (0.94–0.97)	0.91 (0.85–0.95)	0.22 (0.17–0.27)
1,5-AG, μg/mL	15.1 (6.5)	15.1 (6.5)	0.04 (1.2)	5.7 (4.2–7.2)	0.98 (0.98–0.99)	0.98 (0.97–0.99)	0.13 (0.10–0.17)
Fasting glucose, mg/dL	125.5 (29.8)	125.3 (32.7)	−0.14 (17.1)	9.6 (7.3–11.8)	0.85 (0.80–0.90)	0.84 (0.73–0.90)	0.42 (0.31–0.53)
Hb A_{1c}, %	6.3 (0.8)	6.3 (0.8)	0.04 (0.2)	2.0 (1.5–2.5)	0.98 (0.97–0.98)	0.96 (0.92–0.98)	0.16 (0.12–0.19)

[a] Data are mean (SD) unless noted otherwise.
[b] The 95% CIs were bootstrapped with 200 replications.

these biomarkers in research and clinical settings.

References

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Christina M. Parrinello[2]
Pamela L. Lutsey[3]
David Couper[4]
John H. Eckfeldt[5]
Michael W. Steffes[5]
Josef Coresh[2,6]
Elizabeth Selvin[2,6*]

[2] Department of Epidemiology and the Welch Center for Prevention Epidemiology and Clinical Research Johns Hopkins Bloomberg School of Public Health Baltimore, MD
[3] Division of Epidemiology and Community Health University of Minnesota School of Public Health, Minneapolis, MN
[4] Department of Biostatistics University of North Carolina at Chapel Hill Chapel Hill, NC
[5] Department of Laboratory Medicine and Pathology University of Minnesota Minneapolis, MN
[6] Division of General Internal Medicine Department of Medicine Johns Hopkins University Baltimore, MD

* Address correspondence to this author at: 2024 E. Monument St, Suite 2-600 Baltimore, MD 21287 E-mail eselvin@jhu.edu