Defining the risk of microvascular complications associated with diabetes mellitus is clinically important for identifying at-risk individuals and evaluating treatment efficacy. The standard measure of mean glycemia, glycohemoglobin A1c (Hb A1c), is associated with incident microvascular complications among diabetic patients, but this biomarker fails to explain all of the observed risk (1). This has led to the hypothesis that microvascular complications may result not only from chronic sustained hyperglycemia but also from glycemic excursions (1). Therefore, identifying biomarkers that are associated with glycemic excursions has direct clinical significance.

For example, in the landmark Diabetes Control and Complications Trial (DCCT) of conventional diabetes therapy vs intensive insulin therapy targeting low Hb A1c, matching attained Hb A1c across the 2 treatment arms did not produce similar reductions in incident microvascular complications (2). The higher rate of microvascular complications observed in the conventional therapy arm of DCCT may have been due to larger glycemic excursions, as this group had fewer insulin injections per day (3). Indeed, in DCCT, greater variability in an individual’s Hb A1c measurements was associated with a higher risk of microvascular complications (4). Mechanistically, both hyperglycemia and glycemic excursions result in oxidative stress, likely through overproducing superoxide by the mitochondrial electron-transfer chain (5, 6), which generates advanced glycation end products, activates polyol activity, and increases hexosamine pathway flux (1, 7).

1,5-Anhydroglucitol (1,5-AG) is a candidate biomarker for glycemic excursions (8). 1,5-AG is a dietary monosaccharide, similar to glucose, that is freely filtered in the renal glomerulus and subsequently competes with glucose for reabsorption in the renal tubules. In the presence of high blood glucose concentrations, 1,5-AG resorption is reduced and serum concentrations of 1,5-AG decrease. Hence, lower concentrations of 1,5-AG correlate with more frequent hyperglycemic episodes (most commonly postprandial hyperglycemia) and reflect trends over a 1- to 2-week timeline. 1,5-AG is currently marketed for clinical use under the trade name GlycoMark® in the US, despite the limited information regarding its potential role in clinical practice.

Several previous studies have suggested an association between 1,5-AG and diabetic microvascular complications (9, 10) and atherosclerosis (11). However, these studies have been limited in their sample size and the scope of end points that were assessed. In this issue of Clinical Chemistry, Selvin et al. conducted an elegant study that used data from >10000 participants in the Atherosclerosis Risk in Communities (ARIC) population to examine the association of 1,5-AG with prevalent retinopathy, incident chronic kidney disease (CKD), and incident diabetes (12). The study benefited from the prospective follow-up (approximately 20 years) for incident CKD and diabetes. Although 1,5-AG was measured years after sample procurement, the interassay agreement between randomly selected duplicate samples was excellent (reliability 0.99). For the analysis of the association between 1,5-AG and incident CKD, the investigators excluded all patients with a baseline estimated glomerular filtration rate (eGFR) <60 mL·min⁻¹·(1.73 m²)⁻¹, leaving 12083 participants. For the analysis of incident diabetes, 10948 participants were included who were free of diabetes at baseline. Mydriatic retinography was used to diagnose prevalent retinopathy in 9447 participants. Because retinography was available at only one time point, the investigators examined the association of 1,5-AG with prevalent retinopathy. Exposure categories of 1,5-AG were defined according to the assay
also attenuated after adjustment for Hb A1c and fasting glucose, but remained significantly associated with a 5-fold increased risk of retinopathy among diabetic participants. Similarly, low 1,5-AG was associated with a ≥2-fold increase in the risk of incident CKD among diabetic participants; this risk remained significant, although it was also attenuated after adjustment for Hb A1c and fasting glucose. After adjustment for clinical variables, Hb A1c, and fasting glucose, low 1,5-AG was associated with a 22%-42% increase in the risk of incident diabetes among nondiabetic participants. These results provide compelling evidence that glycemic excursions are important predictors of microvascular complications among diabetic individuals, in addition to their association with incident diabetes among nondiabetic individuals.

Although the inverse correlations for 1,5-AG with Hb A1c and fasting glucose were moderate to high (Spearman coefficients −0.77 to −0.84) in the diabetic participants, they were quite low (−0.02 to −0.08) in the nondiabetic participants, suggesting that 1,5-AG could add a new dimension to predicting diabetes. To determine if adding 1,5-AG to predictive models incorporating traditional clinical risk factors and Hb A1c would improve model performance, the investigators calculated two measures of discrimination (namely, the change in the c-statistic and the integrated discrimination-improvement [IDI]) and a measure of risk reclassification (net reclassification index [NRI]). When 1,5-AG was added to these models, there was a statistically significant, although clinically small, improvement in the c-statistic for retinopathy, but not for incident CKD or diabetes. The continuous NRI and IDI with the addition of 1,5-AG showed similar results. Hence, when combined with traditional clinical risk factors and Hb A1c, concentrations of 1,5-AG did not meaningfully improve the predictive model performance for retinopathy, CKD, or diabetes in the overall ARIC study population.

The results of this well-conducted study should be interpreted in the context of the study design. Given that 1,5-AG reflects glucose excursions over a 1- to 2-week time period, relying on a single measurement of 1,5-AG may result in potential misclassification bias, which may weaken the associations. Although the study benefited from long (20-year) follow-up, advances in diabetes care over the study period have occurred, and estimates of microvascular complications may be attenuated in current clinical practice. Additionally, given reliance on intact tubular resorption of 1,5-AG, the presence of worsening nephropathy could potentially alter 1,5-AG kinetics. This question is important clinically, as nephropathy could be due to a number of comorbid conditions, including hypertension, cardiovascular disease, and intrinsic renal disease, and 1,5-AG could potentially be a risk marker for incident diabetes, retinopathy, or worsening renal function from diabetic nephropathy. One previous study showed that 1,5-AG concentration was a good predictor of glycemic control in patients with stages 1–3 CKD; by contrast, in patients with stages 4 and 5 CKD, eGFR had a strong influence on 1,5-AG (13). In selecting a population of ARIC participants largely free of CKD at baseline, in whom only a minority (approximately 5%) had an eGFR <60 ml·min⁻¹·(1.73 m²)⁻¹, Selvin et al. minimized the effects of advanced renal disease on 1,5-AG. Nonetheless, the study leaves open the question of how 1,5-AG might be useful in patients with CKD that is due to nondiabetic causes. It is also uncertain whether medications that alter glomerular filtration—namely, angiotensin converting enzyme inhibitors—could affect the reliability of 1,5-AG measurements. Finally, cutoffs suggested by the manufacturer may not represent the ideal cutoffs for clinical practice.

Overall, this study provides important new evidence that greater glucose excursions are associated with a higher risk of incident diabetes among nondiabetic individuals and microvascular complications among diabetic individuals. Enthusiasm for widespread use of commercially available 1,5-AG assays should be viewed in the context of the model prediction metrics assessed in the study, as 1,5-AG did not add considerably beyond standard clinical risk factors and Hb A1c in the ARIC population as a whole, although it is possible that there are specific subgroups of patients who may potentially benefit from 1,5-AG testing. This well-designed and timely study from the ARIC investigators provides the critical foundation for designing future prospective studies of 1,5-AG and other novel glycemic biomarkers.

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