In some settings, alternatives to HbA1c acceptable

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November 2023—Glycated albumin and fructosamine are highly specific, with high levels suggesting hyperglycemia. This points to their utility in monitoring glycemic control in people with diabetes.

“They’re quite useful in the setting of overt hyperglycemia,” said Elizabeth Selvin, PhD, MPH, professor of epidemiology and medicine, Johns Hopkins Bloomberg School of Public Health, in her “hot topic” presentation at this year’s meeting of the Association for Diagnostics and Laboratory Medicine.

Dr. Selvin is a coauthor of much of the population research on glycated albumin and fructosamine, some of which found them to be associated with prevalent retinopathy, incident chronic kidney disease, incident cardiovascular disease, and all-cause and cardiovascular mortality.

“We found associations of fructosamine and glycated albumin with outcomes were similar in magnitude to hemoglobin A1c, and they’re especially strong in people with diabetes,” she said.

New guidelines and recommendations for laboratory analysis in diabetes diagnosis and management were released just before the ADLM meeting (Sacks DB, et al. *Diabetes Care.* 2023;46[10]:e151–e199). In the guidelines is the following recommendation: Assays of glycated proteins, such as fructosamine or glycated albumin, may be used in clinical settings where abnormalities in red blood cell turnover, hemoglobin variants, or other interfering factors compromise interpretation of HbA1c test results, although they reflect a shorter period of average glycemia than HbA1c.

In addition, the guidelines say HbA1c cannot be measured and should not be reported in those who do not have hemoglobin A (for example, those with homozygous hemoglobin variants such as hemoglobin SS or EE). Glycated proteins, such as fructosamine or glycated albumin, may be used, the guidelines say.

“They may also have use for adjudicating individuals who have discrepant hemoglobin A1c and glucose results. We can break the tie with a third test,” Dr. Selvin said, citing the guidelines and recommendations as “the first guidance we’ve seen from major laboratory or medical organizations on the use of these tests.” The ADLM and American Diabetes Association approved the guidance.

Interest in the use of glycated albumin and fructosamine as alternative markers of hyperglycemia has grown, and the question was whether there are settings in which these biomarkers can be complementary to HbA1c or used when HbA1c is problematic.

Like HbA1c, they’re indirect measures. Fructosamine reflects total glycated serum proteins. Glycated albumin is the proportion of albumin that has glucose bound to it.

They reflect a two- to three-week exposure to chronic hyperglycemia.

Glucose has limitations, among them diurnal variation and the need to be processed quickly or put on ice and for the patient to be in a fasting state or undergo a glucose tolerance test. “It only captures a single moment in time. It’s not an integrated measure,” Dr. Selvin noted. HbA1c overcomes some of glucose’s limitations but has its own.

Dr. Selvin

Fructosamine is available for clinical use but not commonly used as a biomarker of glycemia. “It’s sometimes used when hemoglobin A1c testing is known to be problematic,” Dr. Selvin said. The FDA cleared glycated albumin for clinical use in 2017. It is regularly, though not widely, used in Japan and other countries to monitor short-term control in diabetes.

Fructosamine or glycated albumin may add value for patients with diabetes when used in conjunction with fasting glucose and HbA1c for risk stratification or for monitoring short-term glycemic control such as in response to treatment changes, Dr. Selvin said. From a research standpoint, “there are a lot of situations where we don’t have stored whole blood, so it’s nice to have glycemic markers that we can measure in serum or plasma.” And researchers in shorter, resource-intensive trials want measures that reflect short-term glycemic control.

Why have these tests not seen greater adoption? “Clinical utility is still relatively uncharacterized,” Dr. Selvin said, and studies of associations with glucose and HbA1c and of prognostic value had been in short supply. And until now major medical organizations hadn’t provided guidance.

Dr. Selvin and colleagues have closed some of the gaps by studying the tests’ prognostic value and their performance in screening for and diagnosing diabetes and prediabetes.

They focused on two study populations: the Atherosclerosis Risk in Communities (ARIC) study and the National Health and Nutrition Examination Survey (NHANES), “one of the most important sources of data on the health of Americans,” she said.

In the ARIC study, she and colleagues (in collaboration with Jesse Seegmiller, PhD, DABCC, and Michael Steffes, MD, PhD, of the University of Minnesota Medical School) measured HbA1c, fructosamine, and glycated albumin at multiple points over the lives of its participants. Dr. Selvin and colleagues assayed specimens from NHANES (more than 23,000 stored blood samples) for a full panel of biomarkers, including glycated albumin (in collaboration with Robert Christenson, PhD, of the University of Maryland Medical Center).

“In ARIC, we were able to look at diabetes, retinopathy, chronic kidney disease, cardiovascular disease, and mortality,” Dr. Selvin said, “and in NHANES we looked at diabetes, kidney disease, peripheral arterial disease, and mortality.” In NHANES, her group was able to study how the biomarkers performed in special populations: pregnant women, children, and adolescents. (Her group’s NHANES-related work was funded by the Biomarkers Consortium of the Foundation for the National Institutes of Health. The NIH funded the ARIC-related work.)

She noted first the strong correlation between fructosamine and glycated albumin themselves—an overall correlation coefficient of 0.93. And both are strongly and similarly correlated with HbA1c, “which is why I continue to talk about both of them in the same breath,” she said.

In a study published in 2014, Dr. Selvin and coauthors found fructosamine and glycated albumin to be strongly associated with retinopathy and risk of incident chronic kidney disease, “especially in people with diabetes, with prognostic values similar to that of hemoglobin A1c,” she said. Both assays and HbA1c showed similar risk associations, “but very strong at the high values and less so at low values,” she said. The HbA1c association is more linear, with less flattening out at the low range.

In a study published in *Clinical Chemistry* in 2022, Dr. Selvin and colleagues characterized the associations of glycated albumin and HbA1c with all-cause and cardiovascular mortality. “Glycated albumin is strongly associated with cardiovascular mortality, with very similar association as compared to hemoglobin A1c,” she said. The authors found “strong, robust associations, very high hazard ratios, in the high or diabetic range,” she added (Rooney MR, et al. *Clin Chem.* 2022;68[3]:422–430).

Fructosamine and glycated albumin

Strengths	Limitations
Non-fasting, measured in serum or plasma, highly reliable automated methods available	No established clinical cut points, assays are not standardized
Unaffected by alterations in red cell turnover or genetic variation in Hb	Affected by alterations in serum protein metabolism, adiposity
Reflect short-term (2–3 weeks) of glycemic control	Indirect measure of glycemia
Highly specific for detecting hyperglycemia	Not sensitive enough for diabetes screening or diagnosis

In the same issue of *Clinical Chemistry* was the first published study of the diagnostic performance of glycated albumin in a nationally representative sample of U.S. adults (Fang M, et al. *Clin Chem.* 2022;68[3]:413–421). "This is looking at the ability of hemoglobin A1c and glycated albumin to detect elevated glucose," Dr. Selvin said of the study of serum samples of nonpregnant adults age 20 and older with no history of diagnosed diabetes in the NHANES cohort. "We know that the diagnostic cut point for hemoglobin A1c is highly specific for detecting elevated glucose in the population, but not particularly sensitive," she said. "What we saw is glycated albumin is also highly specific but a little less specific than hemoglobin A1c—but also a lot less sensitive. So hemoglobin A1c outperformed glycated albumin as a general screening diagnostic test in the general U.S. population."

Glycated albumin also did not perform well as a biomarker of hyperglycemia in normal pregnancy. In a study published this year, Dr. Selvin and coauthors evaluated data from 555 pregnant women who participated in NHANES and did not report a pre-pregnancy diagnosis of diabetes. Its conclusion: "GA is not a sensitive test to screen for hyperglycemia in pregnancy." Glycated albumin was poorly correlated with HbA1c and random glucose. "We know that hemoglobin A1c doesn't perform well in pregnancy," Dr. Selvin said. "The glycated albumin and glucose were almost uncorrelated in this setting of normal pregnancies, so it ruled out the idea of using glycated albumin as a screening test for hyperglycemia in pregnancy" (Rooney MR, et al. *Clin Biochem.* 2023;112:67–70).

Dr. Selvin and colleagues also found glycated albumin to be a poor predictor of hyperglycemia in a general, nondiabetic pediatric population. "We found that glycated albumin was almost uncorrelated with hemoglobin A1c and fasting glucose in a general population of children and adolescents," she said, and not an appropriate biomarker for screening (Wallace AS, et al. *Pediatr Diabetes.* 2022;23[2]:237–247).

In both the pediatric and pregnancy studies, glycated albumin was inversely associated with adiposity. "We're not the only ones to show this," Dr. Selvin said, adding the same is true for fructosamine. She and colleagues dug into the question of how glycated albumin is associated with different measures of adiposity (BMI, waist circumference, and others), using stored serum samples from 10,835 adults participating in NHANES. "We show, again, this very strong inverse association between glycated albumin and BMI and consistent across all other measures of adiposity," she said (Sullivan VK, et al. *J Appl Lab Med.* 2023;8[4]:751–762).

As expected, the study authors found positive associations for HbA1c. "We found glycated albumin was lower at the highest levels of BMI in both men and women, whereas hemoglobin A1c has a strong linear association: higher BMI, higher hyperglycemia, higher glucose, and higher hemoglobin A1c," she said.

Why does excess adiposity appear to have a profound effect on fructosamine and glycated albumin? "I really don't know," Dr. Selvin said, noting she's asked others the same question. There might be obesity-related changes in the local molecular environments surrounding albumin that impair glycation, she postulates. "One of the cool things about epidemiology is even if we don't fully know why something is occurring, we can still determine whether it's important." This finding "suggests a limitation of glycated albumin for clinical use."

To sum up, Dr. Selvin pointed to these conclusions:

- Fructosamine and glycated albumin are strongly correlated with HbA1c and fasting glucose, especially at higher values.
- Associations of both tests with outcomes were similar in magnitude to those for HbA1c and especially strong in people with diabetes.
- Excess adiposity appears to have a profound effect on fructosamine and glycated albumin.
- Neither of the two tests is sufficiently sensitive to screen for and diagnose diabetes or prediabetes in the general population, pregnant individuals, or children and adolescents.

But studies do point to their utility in monitoring glycemic control in people with diabetes. “The field is taking note and moving forward,” Dr. Selvin said, “and it’s gratifying to see guidance in terms of how we can use these tests.” However, there is work to be done in establishing cut points, determining how to interpret them, and standardizing the assays.n

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