Latest HbA_{1c} debate examines race as nonglycemic factor

Kevin B. O'Reilly

December 2015—In 2010, the American Diabetes Association endorsed the use of hemoglobin A1c to diagnose type 2 diabetes, and fierce arguments over the wisdom of that move have ensued ever since. A 2013 debate at the American Association for Clinical Chemistry's annual meeting featured a spirited dialogue on the merits of using HbA_{1c} as a diagnostic marker, compared with the traditional—and still ADA-recommended—alternatives, fasting plasma glucose and two-hour plasma glucose.

Now the discussion is zeroing in on a narrower controversy within the HbA_{1c} dispute—the role of race and ethnicity. African-Americans regularly have higher HbA_{1c} values than do whites, even when they have similar fasting plasma glucose levels. Hispanics, too, have exhibited a similar HbA_{1c}/FPG disparity, though amid a smaller body of research and to a lesser degree than is found among blacks. The questions are what this widely observed trend means and what to do about it.

Do higher HbA_{1c} concentrations among blacks and Hispanics reflect socioeconomic or lifestyle factors, or are they driven by some as yet unidentified molecular or biological nonglycemic factors present in these patient populations? Should clinicians and laboratories set different diagnostic cutpoints for their black and Hispanic patients than for their white ones? Should laboratories seek race and ethnicity data to help overcome this apparent impediment to HbA_{1c} interpretation?

These questions and more will come to the fore in an upcoming point-counterpoint on the issue in the ADA's influential Diabetes Care journal. They also arose as part of a provocative, well-attended session at this year's AACC meeting.

Dr. Sacks

David Sacks, MB, ChB, FRCPath, helped organize the session—a version of which also was held at this year's ADA meeting—and in his introductory remarks he provided a contextual understanding of hemoglobin glycation and the nonglycemic factors that have been identified in the medical literature.

"Clearly, there are some factors that influence HbA_{1c} that are independent of glycemia," Dr. Sacks tells CAP TODAY. "There aren't as many as the reviews and the old textbooks have listed because many of the factors that are reported to alter HbA_{1c} may have interfered in old assays—the measurements that we used in the '70s or '80s—but many of these do not occur with current HbA_{1c} assays."

Dr. Sacks, senior investigator at the National Institutes of Health and chief of clinical chemistry at the NIH Clinical Center, notes that HbA_{1c} testing improvements played a big role in encouraging the ADA and the World Health Organization to recommend using HbA_{1c} as a diagnostic test for type 2 diabetes.

"One of the main reasons for saying that it was OK to use HbA_{1c} for diagnosis was actually based on the clinical lab

community, because they [the ADA and WHO] said the test is good enough now," he says. "Before, they said the test is not harmonized and not accurate enough and then they changed. And that's in large part due to the people and the companies who worked hard to harmonize the assay."

So, conditions such as uremia and hyperbilirubinemia—once identified as nonglycemic factors affecting HbA_{1c}—are no longer stumbling blocks.

"There's this one category that interferes with the actual measurement. As the manufacturers improve their methods or new methods are developed, they can eliminate some of these factors. They are basically assay artifacts," Dr. Sacks says. "And then there is another group of factors that are of much greater concern and interest and really do change the value. Those are the ones that require more thought and discussion. Race would fit into that category."

Other nonglycemic factors in this category include age, chronic renal failure, iron-deficiency anemia, red blood cell lifespan, and differing hemoglobin glycation rates, Dr. Sacks said in his talk at the AACC meeting. The impact of race as a nonglycemic factor is particularly fascinating because it has yielded differing interpretations among experts surveying the available body of evidence.

"One of the intriguing things to me is that if you look at the literature on race and HbA_{1c}, while the studies are not designed exactly the same, the question they're asking is the same and yet they come up with completely opposite conclusions," Dr. Sacks says.

And so it was during the AACC session. Endocrinologist William H. Herman, MD, MPH, took first to the lectern to argue the case that race does alter HbA_{1c} independently of glycemia. He cited an array of studies finding differences of between 0.4 and two percentage points in HbA_{1c} between white patients with type 2 diabetes and their black counterparts (Kirk JK, et al. *Diabetes Care*. 2006;29[9]:2130–2136).

Dr. Herman pointed to another study showing that 164 black patients and 1,815 white patients had fasting plasma glucose scores only two points apart (153 mg/dL for African-Americans, 151 mg/dL for whites). Yet the average HbA_{1c} for the two groups differed by 0.7 percentage points—eight percent for blacks, 7.3 percent for whites (Viberti G, et al. *Diabet Med.* 2006;23 [12]:1289–1294).

"These racial differences are not explained by access to care or quality, and they appear to occur independently of glycemia," said Dr. Herman, the Stefan S. Fajans/GlaxoSmithKline professor of diabetes at the University of Michigan Medical School and director of the Michigan Center for Diabetes Translational Research.

"We can't explain why these differences occur," he added. "And I don't think we can or should discard the observation, and the observation is incredibly robust that there remain unexplained differences in hemoglobin A1c between African-Americans and whites."

Dr. Herman

As support for this argument, Dr. Herman cited a study of 1,806 patients covered by Harvard Pilgrim Health Care and receiving treatment at Harvard Vanguard Medical Associates. At the start of the study period, the 467 black patients had an average $HbA_{1c}$of 9.8 percent, compared with 8.9 percent for the 1,339 white patients. After one

year, there remained a 0.5 percent difference in HbA_{1c} even after adjusting for age, sex, body mass index, hypertension, comorbidities, medication adherence, and many other potential confounders (Adams AS, et al. *Diabetes Care.* 2008;31[5]:916–921).

"A lot of the studies have been done to tease out these differences and adjust for these [socioeconomic and treatment] differences, but none of those studies have been able to make those [HbA_{1c}] differences go away," Dr. Herman said.

For Dr. Herman, also a professor of epidemiology and internal medicine, the concern about hemoglobin A1c is far from academic. If there is some unexplained reason why black patients' HbA_{1c} is higher than that of whites, this may prompt overly aggressive medical treatment that could lead to hypoglycemia. He noted a study finding that African-Americans visit the emergency department for hypoglycemia at rates two to four times higher than those of white patients, suggesting that this overtreatment may be happening (Lipska KJ, et al. *JAMA Intern Med.* 2015;175 [3]:356–362).

"Hemoglobin A1c is not glucose," Dr. Herman said in concluding his AACC talk. "It is influenced by red-cell survival and by a number of other factors which, unfortunately, we're not smart enough to understand at this point. The empirical observation stands that HbA_{1c}s are higher in African-Americans than in whites despite similar or comparable glucose levels…. Interventions to reduce racial disparities in hemoglobin A1c must carefully weigh both the benefits and risks."

Dr. Selvin

In taking her turn at the lectern, Elizabeth Selvin, PhD, MPH, did not dispute that racial and ethnic differences are seen in hemoglobin A1c measurements. But, she said, the differences are slight and HbA_{1c} does its principal job of predicting long-term diabetes-related morbidity and mortality.

"In all of these studies, the absolute differences we're talking about in hemoglobin A1c are small. We have a 4.93 percent average in whites, 5.16 in blacks, 5.05 in Mexican-Americans. At the low levels of A1c there are no differences. Actually, what we see is that the differences are primarily driven by the higher level of the range," said Dr. Selvin, professor of epidemiology and medicine at the Johns Hopkins Bloomberg School of Public Health.
"I do agree we see differences," she added. "There is a lot of difference between ethnic and racial groups on various laboratory parameters."

Dr. Selvin offered a potential explanation for the disparities.

"It's possible that differences in activity, stress, the environment, the neighborhood, lifestyle factors, and exposures might influence HbA_{1c} via real differences in nonfasting glycemia," she said. "But this wouldn't be captured in studies that only have a single glucose measure."

In an interview with CAP TODAY, Dr. Sacks speculates along similar lines.

"People, before they go to the dentist, they brush their teeth. People with diabetes, before they go to the doctor, if they've been eating cake and candy and they know they're going to the doctor on Wednesday, maybe for a few days they eat better," he says. "Fasting glucose captures the moment you stick the needle into the arm. HbA_{1c} is a

measure of the last eight to 12 weeks. That's a very useful thing."

For Dr. Selvin, the most valuable aspect of HbA_{1c} is its ability to predict outcomes for patients regardless of their race or ethnicity—for example, the rates at which they develop cardiovascular disease.

"HbA_{1c} is a measure of average glucose," she said. "Glucose is not the right gold standard. The right measure is clinical complications. The way to evaluate it is to look at its prognostic value and its relationship to long-term clinical outcomes."

In a prospective cohort analysis of 2,484 black patients and 8,593 white patients, she and her colleagues found that HbA_{1c} "is a risk factor for vascular outcomes and mortality in both black and white adults" (Selvin E, et al. Diabetes Care. 2013;36:2995–3001). This was their conclusion after adjusting for age, sex, LDL cholesterol, waist-to-hip ratio, and many other potential confounders.

"HbA_{1c} was more strongly associated with these outcomes compared with fasting glucose, and it was similarly prognostic for blacks and whites," Dr. Selvin told the AACC crowd.

"There's no evidence that race is a modifier of the associations between HbA_{1c} and the risk of these outcomes," she added.

"The racial differences in HbA_{1c}, especially at diagnostic levels, likely reflect true differences in hyperglycemia," Dr. Selvin concluded. "Blacks and Mexican-Americans are at higher risk of diabetes and complications compared with whites, and differences in stress, diet, etc., may contribute to higher nonfasting glycemia."

Before the debate began, the standing-room only AACC crowd was asked, by show of hands, to say whether they agreed that race was an independent factor changing HbA_{1c} levels. About a third of those present said yes, another third said no, and the remainder were undecided.

When Dr. Selvin concluded her presentation, the crowd was surveyed again. A few hands went up to say yes, they believed race alters HbA_{1c} independently of glycation. About twice as many said no, it does not. But the vast majority of the laboratory professionals now said they were undecided, a testament to the power of the presentations and how much remains to be learned about the phenomenon of race, ethnicity, and hemoglobin glycation.

During the question-and-answer session, Dr. Selvin speculated that certain elements of what is happening may be beyond the ability of epidemiology to capture.

"Epidemiology is not physics," she said. "We're observing human beings in their natural settings, and understanding the inherent variability in biomarkers is very important."

"I'm from Baltimore," Dr. Selvin added. "There are major differences in the experiences of African-Americans and whites. Anyone who's been pulled over by a cop can tell you that. We really need not to discount that. These are differences that we can't adjust away in epidemiological studies. These are differences that go back to the historical origins of our country."

Drs. Herman and Selvin did agree that more research involving continuous glucose monitoring, rather than fasting plasma glucose tests, could help answer some of the questions at issue in the session.

"One could design a good study that could evaluate that, and I think it would be important to design such a study to have enough individuals to have statistically significant results so you could interpret it, and have a diversity of individuals—healthy people, lots of type 2 diabetic individuals, maybe some type 1s who are stable and control their glucose well," Dr. Sacks tells CAP TODAY. "Funding the study would be a big problem. It does have intellectual appeal, but the key question is whether this is more important to study than something else."

In an interview, Dr. Herman says even that type of study would not resolve all the concerns he has about how HbA_{1c} appears to differ by race and ethnicity.

“What I’m actually beginning to find increasingly frustrating is that there is this debate, but very little progress toward scientific resolution,” he says. “I say what I think, she [Dr. Selvin] says what she thinks, but neither of us has the definitive data to answer the question.”

“There are lots of epidemiological questions to look at, but we need to drill down to the basic scientific and molecular level, which is certainly beyond my expertise,” Dr. Herman says.

To Dr. Selvin, the back-and-forth on this question could have thoroughgoing consequences.

“The stakes are high because what the other side’s arguing is that hemoglobin A1c in African-Americans is artificially high. Take that to its logical conclusion…and that means we should use a higher cutpoint in blacks,” she says. “But I don’t see who’s concerned about overdiagnosis of diabetes in African-Americans. African-Americans have a much higher risk of complications, a higher risk of diabetes, and poor access to care. The idea that we should be more conservative in diagnosis concerns me.”

Dr. Herman says he is not seeking a different HbA_{1c} cutpoint for African-American or Hispanic patients. For now, he resolves his concerns by seeking multiple measures to confirm a diagnosis.

“I try to mix it up a little,” he says. “If the screening test is A1c, I will follow up with fasting glucose because I can deal with uncertainty. I’d rather think about it and say, ‘Which test do I really believe?’ As a routine practice, before I label someone as diabetic I will confirm with another test, and usually use fasting glucose and A1c—a combination of the two rather than just one.”

Dr. Herman tells his endocrinology residents and fellows to look at multiple measures of glycemia “and if there’s a discrepancy between them, think which is right, why the discordance is there, and not to rely solely on one test.”

At the moment, it appears there is little to discourage Dr. Herman or any clinicians so inclined from taking this approach to diagnostic testing for type 2 diabetes. The NIH’s Dr. Sacks delivered the big picture in closing his AACC talk.

“Hemoglobin A1c can be measured accurately in the vast majority of patients, and it provides valuable clinical information for most individuals,” he said.

“Is HbA_{1c} the perfect test? No,” he tells CAP TODAY. “But neither is glucose or anything else.”

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