HbA1c shows its mettle in predicting diabetes risk

Anne Paxton

December 2017—The longitudinal Framingham Heart Study, which first identified the concept of risk factors and made serum LDL cholesterol a household name, could help increase the celebrity status of HbA_{1c}, with the Oct. 26 publication of a new study in *Diabetes Care*.

International and national organizations since 2010 have recognized HbA_{1c} as a valid way to diagnose abnormalities in glycemia and diabetes mellitus. But there has been less consensus on its use as a screen for elevated diabetes risk.

It has been shown that elevated HbA_{1c} and elevated fasting glucose are better at diabetes prediction than fasting glucose alone. But is HbA_{1c} associated with incident diabetes independently, such that HbA_{1c} results can identify individuals with high diabetes risk? That was the question addressed in the *Diabetes Care* retrospective study "Prediction of type 2 diabetes by hemoglobin A1c in two community-based cohorts," in which the authors reviewed extensive data collected on subjects of the Framingham Heart Study and the Atherosclerosis Risk in Communities (ARIC) study (Leong A, et al. doi.org/10.2337/dc17-0607).

Based on that data, the authors found that HbA_{1c} predicts diabetes in different common scenarios and is useful for identifying individuals with higher diabetes risk in the short and long term. HbA_{1c} is an "accurate and convenient test [that] has a central place in Type 2 diabetes prevention efforts nationally and worldwide," the authors conclude.

The *Diabetes Care* study "is one of the first to demonstrate the additive value of HbA_{1c} in improving the ability to diagnose future diabetes mellitus in combination with fasting glucose," says study coauthor Michael J. McPhaul, MD, medical director for endocrinology and metabolism at Quest Diagnostics' Nichols Institute.

For this study, the researchers focused on middle-aged participants in the Framingham and ARIC studies who did not have diabetes—11,244 whites and 2,294 blacks—and determined whether those subjects developed diabetes in the short term (within eight years) or the long term (after 20 years). A total of 3,315 subjects developed diabetes after 20 years, and their initial HbA_{1c} results, it turned out, were highly predictive of whether they did develop diabetes. For each percentage-unit increase in HbA_{1c}, the odds of developing diabetes increased fourfold.

Those results held in four real-world scenarios where HbA_{1c} is commonly used: the "HbA_{1c} only" scenario in which age and sex are the only extra factors taken into account; the "HbA_{1c} plus fasting laboratory tests" scenario; the "HbA_{1c} plus clinic visit" scenario; and the "HbA_{1c} plus fasting laboratory tests plus clinic visit" scenario. In all of these models, higher HbA_{1c} was associated with increased type 2 diabetes risk in participants, with and without high fasting glucose.

The study authors' intent was not primarily to demonstrate that HbA_{1c} predicts diabetes, says study coauthor James B. Meigs, MD, MPH, professor of medicine at Harvard Medical School and one of the investigators of the Framingham Heart Study. "We knew when we started that HbA_{1c} predicts diabetes, so that was our 'straw-man' hypothesis. In this paper, we wanted to frame the study around how well HbA_{1c} predicts in common clinical settings. We showed it did work in all the settings we examined."

"We concluded HbA_{1c} is a useful test; there are different scenarios where people get tested with HbA_{1c}, and it works in all. So let's use it."

HbA_{1c} and fasting glucose measurements, while typically concordant, are sometimes discordant, and the importance and implications of that discordance have not been systematically studied, Dr. McPhaul points out. If the two measures were represented by circles in a Venn diagram, their sets of results would largely overlap, but there would be slivers on either side representing cases in which one result but not the other indicates diabetes or "normal."

At Quest, Dr. McPhaul's charge is to update and improve on existing offerings in the areas of diabetes and metabolic disorders, and he has collaborated with other institutions to explore the relationships of different measurement phenomena in diabetes. The new study is the result of a collaboration with Dr. Meigs.

"We decided to model the utility of adding HbA_{1c} to the existing diabetes risk score, which is one of a number of calculated algorithms created as a spinoff of the Framingham cohort study," Dr. McPhaul says. "It's a relatively simple algorithm that integrates a number of demographic features, including diastolic hypertension and family history of diabetes, to give a risk score for developing diabetes within eight years."

Dr. McPhaul

When first developed in 2007, that risk score did not include HbA_{1c}. "I always found that kind of puzzling," Dr. McPhaul says. So he and other researchers began to look at how much the change in the capacity of HbA_{1c} would change the overall predictiveness of the algorithm. "We also decided to look at HbA_{1c} as an independent variable. We simply analyzed the data in a way that allowed us to include all the elements that were part of the original Framingham score, but also kept a measure of how well and in what way HbA_{1c}, as an independent variable, would affect the risk over time."

The researchers decided to use four typical screening scenarios for this analysis. "We didn't want some arcane, highly constrained single view of the way to see the impact of these different parameters," Dr. McPhaul says. Several of the different models borrowed from the original Framingham risk score to include demographics, laboratory data only, or both. Conducting a retrospective analysis of data and information that was collected prospectively, "we added into this the HbA_{1c} measure to see what impact HbA_{1c} would have on the model." The goal was to find the best combination for providing a cost-effective means of assessing diabetes risk, with a minimum of material information needed to add into the model.

Fasting glucose and HbA_{1c} are different angles on exactly the same problem, Dr. McPhaul says. "Fasting glucose is a snapshot, looking at people under the best of all possible circumstances, of how well their body can regulate and maintain glucose at a normal level, while HbA_{1c} is a very specific correlate to an average glucose over time." The *Diabetes Care* study brings into focus that these two pieces of information are not simply interchangeable; each contains information that complements the other, he says.

An early surprise of this research project was the predictive capacity of HbA_{1c} in subsets of individuals who had no element suggesting they were going to have diabetes in the future, based on other risk factors. "You could see that there were people who were predicted to be at risk who did develop diabetes, but have normal fasting blood sugar." Dr. McPhaul has heard physicians say to patients in the past that slight elevations of HbA_{1c} don't have consequence. But "I don't think slight elevations of HbA_{1c} have necessarily been viewed as they should be viewed, which is as an early warning sign."

The *Diabetes Care* study showed that individuals with normal HbA_{1c}, whatever their other test results, are at the lowest risk of developing diabetes and people with the highest HbA_{1c} have the highest risk, Dr. McPhaul says. “Whether you’re black, whether you’re white, whether you were in ARIC, whether you were in Framingham, these observations hold true in both of these very large cohorts.” Given these findings for two racially diverse cohorts, he adds, “I have no reason to believe that these observations would not be true if modeled on any other similarly sized population of whatever ethnic or racial composition.”

Addressing the controversy among international groups over the best role for HbA_{1c} in identifying risk was beyond the scope of the *Diabetes Care* study, Dr. McPhaul notes. “What the study does point to clearly is that abnormal HbA_{1c} is something that people should pay attention to. Even if a screening result includes only a moderately elevated HbA_{1c}, people should take that seriously and recognize that they should be even more urgent and direct in addressing their risk factors through improving their level of exercise and decreasing their weight.”

The study authors compare the use they recommend for HbA_{1c} to the uses of prostate-specific antigen and LDL. Since the risk estimates and prediction equations were obtained from large population-based cohorts from two major U.S. ethnicities with two decades of follow-up, HbA_{1c} results “can be used in clinical laboratory reports, similar to the reporting of high values of PSA and LDL that are supplemented by their associated estimated risk for prostate cancer or cardiovascular disease,” the study notes.

This comparison is simply a matter of recognizing that the risks and benefits of HbA_{1c} are ones that have to be judged carefully within the context of the decisions to be made, Dr. McPhaul says. “The measurements of lipids or PSA can be judged as valuable enough to warrant their use in specific circumstances: the evaluation of patients. In the case of HbA_{1c}, it should be recognized as not simply an equivalent of fasting glucose but something that can add to the information that fasting glucose provides.”

Dr. McPhaul also believes that the *Diabetes Care* study solidly makes the case for the contribution of HbA_{1c} to risk assessment. “The breadth of population that has been studied here pretty well establishes that this is not a one-time observation and one study. It demonstrates that individuals with elevations of HbA_{1c} have the highest risk of future diabetes no matter what their glycemic status is.”

But the greater utility of research like the *Diabetes Care* study will be getting people to pay attention to the test results, Dr. McPhaul says. “The challenge is not really research. It’s more implementation: getting physicians and patients to act on the data they have in front of them through diet and exercise. That’s the need we have in front of us as a society, so we don’t end up spending the equivalent of the GDP of Greece on diabetes every year.”

Since the American Diabetes Association and the World Health Organization recommended HbA_{1c} for screening and diagnosis of diabetes in 2010 and 2011, respectively, “we’ve seen major increases in HbA_{1c} testing and its use for diagnosis,” says Elizabeth Selvin, MPH, PhD, a coauthor of the study and a professor of epidemiology at Johns Hopkins Bloomberg School of Public Health, who has published extensively on HbA_{1c} and the epidemiology of prediabetes and diabetes. “But for prediabetes, the subject of the *Diabetes Care* study, there is much more controversy regarding an optimal single definition.”

To start with, there is no universally agreed-upon definition of prediabetes. The ADA and WHO recommend different ranges of fasting glucose results to define who has prediabetes. Although the two organizations do agree on ranges for two-hour glucose, Dr. Selvin notes, that test is not used as widely as the other tests. “So in the end, that means there are five different definitions of prediabetes that are currently employed. And that’s definitely sowing confusion in this field.”

Dr. Selvin

The commonly held belief that one-quarter to one-third of diabetes cases are undiagnosed is a misconception in the literature, according to another new study published Oct. 24 in the Annals of Internal Medicine, led by Dr. Selvin ("Identifying trends in undiagnosed diabetes in U.S. adults by using a confirmatory definition: a cross-sectional study"; doi:10.7326/M17-1272).

"Almost exclusively, prior studies of the prevalence of undiagnosed diabetes have relied on looking at single elevated fasting glucose, elevated HbA_{1c}, or elevated two-hour glucose, and if you have an elevated fasting glucose and no other indication, they classify it as undiagnosed diabetes. This is not consistent with guidelines from our major diabetes organizations, which state that an elevated test result should always be confirmed with a second test." The implication, Dr. Selvin points out, is that prior studies have overestimated the prevalence of undiagnosed diabetes.

The problem with prior epidemiologic studies is that they do not use definitions of undiagnosed diabetes using confirmatory testing. "A person with elevated glucose of 127 but normal HbA_{1c} would not be classified as having diabetes in clinical practice, yet our epidemiological studies say that person has undiagnosed diabetes."

In reality, using definitions of undiagnosed diabetes that are more consistent with clinical practice, "we see that undiagnosed diabetes is fairly uncommon. Our study suggests that health care providers are doing a good job with screening and diagnosis." While it's true that diabetes is at epidemic proportions, Dr. Selvin adds, people who have diabetes are largely being identified in clinical practice.

Many of us have published a lot of papers on the question of whether HbA_{1c} is as good a predictor as glucose, and have examined the question of where does HbA_{1c} fit most usefully in clinical care," says Dr. Meigs, co-director of the clinical effectiveness research group at Massachusetts General Hospital. "Quest was interested in collaborating on this because they have an HbA_{1c} assay and were interested in a paper that would get specifically at the information utility of HbA_{1c} in various health settings."

In fact, Quest service centers are one place where people might go to get a blood test and have only an HbA_{1c} performed; that's the first of the four scenarios the authors considered (HbA_{1c} only). "Another scenario is 'come see me in my office today,' where you would take a medical history, draw a spontaneous, nonfasting blood test, including an HbA_{1c} level. The clinic visit is a more information-rich environment than a clinical lab service center," Dr. Meigs says.

The authors decided that since the question was big enough, "we would use two different, representative population studies where there are lots of cases of diabetes and lots of measurements of HbA_{1c} and careful follow-up." Framingham has the advantage of including middle-aged participants, right around the age where people develop diabetes, "but everyone in it is white," Dr. Meigs says. "ARIC, although the visits are a little less frequent, has a black population, younger people, and lots of long follow-up. And they're generally comparable studies, so we were able to use them together to combine some of the models to get a robust estimate of the marginal information value of HbA_{1c} using all of the test results."

Dr. Meigs

One of the most important findings is that in all four scenarios studied, HbA_{1c} improved prediction or improved discrimination, he says. “Discrimination is expressed in the so-called c-statistic, or concordance statistic, which is a probability that if you have two people in front of you, you can guess which one has higher risk. If the probability is 70 or 80 percent, which is the kind of value we were getting in our models and our papers, then that is clinically useful. Then the question we asked—if you add HbA_{1c}, are you even better at assessing risk?”

For comparison, Dr. Meigs notes, the criterion standard in the field is the Framingham heart attack prediction model, which takes age, sex, smoking, diabetes, cholesterol levels, and blood pressure and returns the probability of having a heart attack. The discrimination of that model is about 75 percent.

It’s hard to improve a c-statistic, he says. “You need a marginal information that is high—higher than most tests we have. HbA_{1c} does improve the c-statistic just a little bit, but it is significant because it is a strong diabetes risk factor.” The meaning of adding a test like HbA_{1c} to the mix has to be contextualized in terms of how bad for health the condition is that you’re looking for, he points out. “Type 2 diabetes is increasing in frequency and leads to very poor health outcomes, so we think that anything that demonstrably improves our ability to find people at risk is a good thing.” This is one reason the study’s conclusion is that HbA_{1c} has definite clinical uses in a range of scenarios.

The *Diabetes Care* study includes additional useful information for those exploring different clinical scenarios. “We published online a huge supplement to this paper giving the parameters of every single model we ran” for providers who want to know what model to use to detect diabetes in their settings. “You’d need a computer to do this. But you can take the parameters and use the regression equations we’ve published to estimate for a person what their risk would be.” Judging from his past published papers, Dr. Meigs explains, “People are interested in programming the values in the models into their own system, for prediction or to compare their model outputs with ours.”

The two cohorts of the Framingham and ARIC studies, with their extended follow-up, were important to the study. “Diabetes is a disease that takes a while to present itself, and if you want to really understand its prediction,” Dr. Meigs says, “having 20 years of follow-up will show the long-term predictiveness of a test. But we also looked at the short term. If you’re an 18- or 20-year-old person, you might have one encounter with the health care system, then not show up again for five or 10 years. We wanted to know if you measured HbA_{1c} once, even a long time ago, does it still predict? HbA_{1c} does predict; it provides a very good picture of diabetes risk over the short term and the long-term future.”

One reason is that HbA_{1c} is an excellent biomarker. “The test is very biologically stable.”

For that reason it can serve different purposes. “HbA_{1c} can be used for screening people to diagnose diabetes and get them into treatment. In treatment, it can reveal your average blood sugar so that today we can decide whether we want to change treatment or change prevention strategy. We can also use it to ask, if we measure this now, what are the chances you’ll get the disease in the future on the basis of the test, and can that information be used to reduce the chances of getting diabetes?” LDL cholesterol testing for heart attack is used in similar ways, he notes.

Dr. Meigs is cautious in predicting the impact of a study like this one on clinical care. “We’re modeling what people

are actually doing, where such data have been hard to come by. Certainly a common practice is that people use the test as part of routine screening annually for people they are worried about as being at risk of developing diabetes. We studied particular scenarios reflecting what people are already doing. If we'd found that in certain areas the test really wasn't useful, then we would have been arguing for a change in practice. I think what we wind up saying with the *Diabetes Care* paper is, however you end up using it, HbA_{1c} is a useful test, and here's the range of its utility in terms of prediction and discrimination."

But the *Diabetes Care* study could help in establishing thresholds for prediabetes, Dr. Meigs says. "The thresholds for establishing the different states of diabetes and prediabetes are arbitrary and decided by expert committees. They draw a line across what are often normal distributions, and say above and below some value is good or bad for health, and people still argue about those values."

"In all fairness, they are reasonable values. They're based on evidence of complications of diabetes increasing at certain values. There's no hard threshold in any of this risk, and for some complications there's an inflection point where rates start to be higher than is acceptable. What we're showing here in this paper is that, even within the ranges people are saying are safe, there is still some risk. Within the range of prediabetes, there is gradation of risk as well, so if your HbA_{1c} is starting to get closer to the diagnostic threshold, the risk is very high. We're saying that if you find a person with a value that is close to the threshold, that person is very likely to progress over the line, compared to a person with slightly lower values."

The study will be useful, he predicts, when people inevitably argue about what the right thresholds are for screening and treating. "We've not just published the equations, but we've also split up the distributions into some finer gradations and are able to show in some of the paper figures this greater increased risk." In addition, the study identifies how many people could be expected to fall into these risk groups, "so if a health plan is deciding which people it should focus on when doing screening, we give some information to guide that decision."

As possible follow-up research to the study, Dr. Meigs says, a next step "is getting bigger cohorts and studies that are not white. ARIC does offer a good population of African Americans in the U.S. But the chronic problem in health epidemiology and population science is the absence of minority subjects in studies, so a more representative sample of African Americans is needed, and then further, Latinos, Asian Americans, East Asians, South Asians, and so on."

A paper by Aaron Leong, MD (of Massachusetts General Hospital and first author of the *Diabetes Care* study), and Drs. Meigs and Selvin and others, published Sept. 12, reveals the danger of ignoring possible genetic differences in interpreting HbA_{1c} results (Wheeler E, et al. *PLoS Med.* 2017;14[9]:e1002383).

"People with a certain mutation, carried by about 11 percent of people of African ancestry in America, have HbA_{1c} values on average that are almost one unit lower than people without it. If you screen them using the approaches we talk about in our community-based cohort papers, you're going to miss them." In the *Diabetes Care* study, Dr. Meigs says,"we don't get into this threshold issue. We just say the models work equally well. And that's fine for a population, but when you're looking at an individual patient, it might matter if they have a genetic mutation." How to bring this complication into practice is a problem with which the field is still struggling.
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