Could CGM dethrone HbA$_{1c}$ for office-based diabetes care?

Anne Paxton

December 2018—A glucose sensor the size of a quarter placed on the body and a sensor filament inserted under the skin could potentially disrupt traditional diabetes care with its continuous monitoring of glucose almost 300 times a day.

Blood glucose can fluctuate widely during the day even in completely healthy people, said David Sacks, MB, ChB, chief of clinical chemistry services in the Department of Laboratory Medicine, National Institutes of Health, in an interview with CAP TODAY. "With CGM, the patient can monitor glucose continuously over days by getting a reading every few minutes."

The implications of CGM for HbA$_{1c}$, long respected as a marker of the risk of complications from diabetes, are beginning to emerge, as studies show the devices can help patients avoid hypoglycemia and lower their average blood glucose concentrations. Endocrinologist Richard Bergenstal, MD, speaking in a session on refining measurement of HbA$_{1c}$ at this year's AACC annual meeting, gave audience members and Dr. Sacks, the moderator, cause to wonder: "Is this the beginning of the end of HbA$_{1c}$?"

Dr. Bergenstal

Dr. Bergenstal, executive director of the International Diabetes Center at Park Nicollet Institute in Minneapolis, is one of a growing number of experts who believe that single HbA$_{1c}$ results of a patient may be telling only part of the story. "In the clinic, A$_{1c}$ is missing a lot of the key elements we need for day-to-day management of diabetes," Dr. Bergenstal said in his presentation, "What HbA$_{1c}$ Results Don't Tell You."

"Since 1993," when the 10-year Diabetes Control and Complications Trial was completed, "we've really been living in an A$_{1c}$ era," he said. "It's a good population health measure. It's a good accountability measure. We use it every day in the clinic where I live." But "Is the A$_{1c}$ the be all and end all, end of story?" He doesn't think so. The goal of his talk, he told the audience, was "to move you past A$_{1c}$ into the world of CGM."

HbA$_{1c}$ is used to diagnose diabetes, to evaluate how effective therapy is, and, probably most important, to predict the risk of irreversible complications, Dr. Sacks notes. "If a patient just sticks a finger, that only tells the glucose at the second when the blood was drawn, and that varies a lot at different times of the day." HbA$_{1c}$, on the other hand, reflects the average glucose over the preceding two to three months. "That's because glucose goes into the red cells, binds the hemoglobin, and the glucose molecule gets irreversibly stuck onto the hemoglobin forming this molecule called HbA$_{1c}$."

The current guidelines for almost all clinical organizations are that individuals with type 1 or 2 diabetes have their HbA$_{1c}$ measured at least twice a year and more often if there is a change in therapy or if the patient is not meeting therapeutic goals, Dr. Sacks says.

But HbA$_{1c}$ is imperfect because factors other than glucose can alter it. Analytic factors make up one group; they

can interfere with measurement and usually can be addressed by use of a different method. "The second group of factors are more of an issue. They are things that change the HbA_{1c} and have nothing to do with glucose," he notes. Race is one factor because there is convincing evidence that African Americans have higher HbA_{1c} than Caucasians. Other factors include iron deficiency or chronic kidney disease. "Are the changes these factors make in HbA_{1c} clinically meaningful? There are studies ongoing to resolve this question. It's become a very important topic that people weren't aware of 20 years ago," Dr. Sacks says.

Clinicians in many countries are increasingly using CGM to estimate HbA_{1c} in addition to measuring it in the laboratory, he says. He compares this to estimating glomerular filtration rate in addition to measuring creatinine to measure kidney function. But clinicians and patients are often confused when the estimated HbA_{1c} (derived from CGM) and the laboratory-measured HbA_{1c} differ. Thus, "estimated HbA_{1c}" is not the term that will be commonly used in the future. Glucose management indicator is the new term preferred by the Food and Drug Administration. Dr. Bergenstal and Dr. Sacks are coauthors of a paper explaining the GMI, published in November in *Diabetes Care* (Bergenstal RM, et al. 2018;41:2275–2280).

A_{1c} certainly correlates with bad things happening, even on the large vessel side," Dr. Bergenstal pointed out in his AACC presentation. "For every one percent increase in the A_{1c}, there is a 17 percent higher chance of a patient having her first stroke, or 49 percent higher chance of having an ischemic stroke in people without diabetes, and a 24 percent increase in stroke in people with diabetes."

HbA_{1c} is also an important regulatory metric—for example, when it's used to compare the performance of new drugs in improving A_{1c}. "And now clinicians are being paid to achieve a certain A_{1c}, so it's a reimbursement metric as well."

But, Dr. Bergenstal noted, "We can't quite agree in the diabetes community on what the goal is for A_{1c}. Is it six and a half? Is it seven? Is it eight?" The value of lowering HbA_{1c} is clear when you are talking about reducing microvascular complications in type 1 and type 2 diabetes. "But there is a little more question when you talk about cardiovascular disease and mortality," he said. "One large study even finds if you try to get an A_{1c} that is perfectly normal, in some situations that can actually increase mortality."

Even if the community could agree on a goal, HbA_{1c} still falls short as a guide to managing patients, Dr. Bergenstal said. "A_{1c} might be a good risk marker overall for the population, maybe even for an individual, but it doesn't really help me get a better A_{1c}."

In fact, he suggested, "Maybe it's not just the absolute level of A_{1c}" that is increasing the chances of complications. "Maybe it's how much that A_{1c} varies over time." Variability in the measurements of HbA_{1c} has been shown in some studies to be a stronger predictor of risk of complications than just the absolute mean of the HbA_{1c} over time, he said.

That's one of the reasons Dr. Bergenstal's clinic is studying the data it's collecting from continuous glucose monitoring of patients. Displaying a chart tracking patients' blood glucose levels from midnight to midnight, he pointed to one patient who had 25 percent of glucose values from 2 AM to 4 AM down near 50 every night, on average, for two weeks. Those data clearly mean one thing to him: "I've got to address those low blood sugars that could kill this patient or result in a coma or something else. I don't care what their A_{1c} is," he said.

Similarly, a comparison of three patients with the same HbA_{1c} showed strong differences in their glucose variations. One was taking four injections a day, one used a pump to deliver insulin, and the third was in a recent trial at the clinic of a so-called artificial pancreas (using computer-driven algorithms to inject insulin based on what the glucose is). "Their glucose fluctuations are completely different. So is their rate of hypoglycemia and their time in range—a measure we're talking a lot about, meaning how much time do you spend in the target range." These variations raise a key question: "How did they get these different levels of improvement with the same A_{1c} but a

more unstable glucose profile?"

His clinic uses such day-to-day data to study people with type 1 diabetes and, increasingly, people with type 2 diabetes. "We're starting to look at CGM very early in the diagnosis as well. You can look at each patient's data and see each one has their own story. I know we've talked about precision medicine in cancer, but this is precision medicine in diabetes. You can look at a picture of the data and know what to do."

Dr. Bergenstal is convinced that CGM addresses a broader range of issues than just HbA$_{1c}$. "There are more than just long-term complications with diabetes. There are day-to-day short-term complications such as hypoglycemia. There is a lot of burden to living with this disease that A$_{1c}$ doesn't really get to."

He is eager to see researchers have a standard way to look at and describe the data. "We need a CGM standardization project. The A$_{1c}$ is a great marker of long-term complications. But CGM is better for short-term complications, easing the burden of diabetes, quality of life, better guiding you in personalizing management, and helping us individualize our targets."

Dr. Sacks

CGM provides a huge amount of information that can be useful, Dr. Sacks says, but the downside is its expense. "You have to get this needle, you have to put the needle under their skin, and then you have to change the needle periodically and patients need to be very motivated." For example, studies show it doesn't work well in most teenagers, he says. "And many countries—I would say most countries—cannot afford CGM for many patients with diabetes."

Estimating HbA$_{1c}$ via CGM is also not a substitute for measuring it in the laboratory, Dr. Sacks emphasizes. "The CGM is used for estimating how much insulin to give." Patients with diabetes have been taught for years to know their ABCs: A (HbA$_{1c}$), B (blood pressure), and C (cholesterol). "So most clinicians can talk to their patients and say, based on their CGM over the last month, what their estimated HbA$_{1c}$ would be." But whether estimated HbA$_{1c}$, or the glucose management indicator, is a better predictor of complications than laboratory HbA$_{1c}$ has not been studied yet, Dr. Sacks says. Answering that question will require a long-term trial with millions of dollars of funding.

Since the AACC meeting last summer, Dr. Bergenstal tells CAP TODAY, two studies have been published showing good correlation for the time patients spend in the target range, based on CGM, and eye and kidney complications (Beck RW, et al. *Diabetes Care.* Published online Oct. 23, 2018. doi:10.2337/dc18-1444; Lu J, et al. *Diabetes Care.* 2018;41[11]:2370–2376). "While not the definitive long-term study Dr. Sacks is looking for," he says, "it is early data showing the potential value of CGM in predicting diabetes complications."

Dr. Bergenstal agrees that continuous glucose monitoring is expensive. "But it is getting better and simpler. Now some of the devices require no calibration. It costs $120 a month to have continuous glucose data and it can go straight up to the cloud" to be shared with clinicians, who could eventually confer with their patients online much more efficiently than through office visits. He thinks the expense also has to be weighed against many benefits. Already at his clinic, for example, "some patients on continuous glucose monitoring are stopping medications costing $600 a month that we thought were working, but weren't," he said.

With continuous glucose monitoring, Dr. Bergenstal said, "It's looking like the whole office-based model of diabetes care needs to change."

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