Hemoglobin A_{1c} May Become Moot

BY MIRIAM E. TUCKER
Senior Writer

The days of hemoglobin A_{1c} reporting may be numbered.

If the final results of the 11-center International HbA_{1c}/Mean Blood Glucose (MBG) Study demonstrate that hemoglobin A_{1c} levels can be mathematically correlated with equivalent mean blood glucose levels in all diabetic populations, a decision could be made as early as 2008 for laboratories to drop A_{1c} entirely and simply report patients' mean blood glucose instead.

For many in the diabetes community, the move would be a positive one. "People can relate to average blood glucose. The term hemoglobin A_{1c} is extremely confusing," said Richard Kahn, Ph.D., chief scientific officer of the American Diabetes Association (ADA).

But any decision to change the way glycemia is reported will be made very carefully, with full awareness of the potentially enormous impact on physicians and patients, according to Dr. David B. Sacks, a pathologist at Brigham and Women's Hospital and Harvard Medical School, Boston, who has been involved in the process from the laboratory medicine side. "We don't want to scare people. Nothing will be changed without people being notified and given lots of preparation time."

Preliminary study data suggest a correlation tight enough to provide an equation to translate HbA_{1c} values to equivalent mean blood glucose, Dr. Robert J. Heine, director of the Diabetes Center at Vrije University, Amsterdam, reported in December at the International Diabetes Federation (IDF) meeting in Cape Town, South Africa. Interim data will be presented at the American Diabetes Association's annual Scientific Sessions in June 2007 in Chicago, and final results will be announced at the annual meeting of the European Association for the Study of Diabetes (EASD), to be held in Amsterdam in September 2007.

The study was prompted by the recent adoption of a new reference method for the measurement of hemoglobin A_{1c} in human blood by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). Whereas previous assays utilized only high-performance liquid chromatography (HPLC) to separate glycated from nonglycated hemoglobin, the new method adds a second step involving mass spectroscopy, which further filters out various glycated peptides that are not actually A_{1c} (Clin. Chem. Lab. Med. 2002;40:78-89).

The result, a more "pure" measure of HbA_{1c}, is about 1.3%-1.9% lower: A 7% with the old reference method, for example, is 5.3% with the new IFCC method, Dr. Sacks said.

Realizing that a switch to reporting the new numbers would likely generate mass confusion, the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation convened a 14-member working group in 2004 to determine how to proceed. Early on, they agreed unanimously that the same HbA_{1c} values should be reported globally and that laboratory instrument manufacturers should not make any changes to the current method of A_{1c} reporting until sufficient data could be collected to link HbA_{1c} with mean blood glucose. Planning for the International HbA_{1c}/MBG Study subsequently began in January 2005.

The new two-step IFCC reference method has been in place for about a year. It is not used with actual patient samples because of cost and time constraints. Rather, manufacturers use the values generated by it to calibrate their laboratory A_{1c} assays, which for the time being are still programmed to report the familiar A_{1c} numbers. But those settings could be changed, depending on what the working group decides.

Among the options the working group will consider, switching to mean blood glucose reporting alone appears to be the most likely if the results of the International HbA_{1c}/MBG Study are definitive. A collaboration of the ADA and the EASD, the study is "supported by generous educational grants" from Minimed-Medtronic, Lifescan, Hemocue, Sanofi-Aventis, Abbott Diabetes Care, GlaxoSmithKline, Bayer, and Merck & Co. It involves 300 patients each with type 1 and type 2 diabetes and 100 nondiabetic subjects from six U.S. cities, the Netherlands, Italy, Denmark, India, and Cameroon.

Glycemia is measured by a continuous glucose monitoring system (CGMS) for 2 days every month for 4 months, along with an eight-point self-monitoring daily profile during the CGMS days. Subjects also perform self-monitoring of blood glucose four times daily for a minimum of 3 days a week. Hemoglobin A_{1c} is measured every month for 4 months.

The aim is to establish the mathematical correlation between A_{1c} and mean blood glucose across diabetes types, genders, and ethnicities. Although there are existing data correlating HbA_{1c} with mean blood glucose—and indeed, many laboratories currently report both numbers—those values were generated from old studies using only infrequent finger-stick monitoring, Dr. Heine explained at the IDF meeting.

If the mean blood glucose study does not generate adequate data—or if other factors intervene—the working group will consider other options. The simplest would be to do nothing, leaving the current A_{1c} values in place. While that would mean continuing to report numbers that aren't totally accurate, it would have the distinct advantage of not rocking the boat.

Moreover, the current A_{1c} values are directly traceable to outcomes from both the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study, allowing for risk assessment for the diabetes-related complications observed in those landmark trials.

Far less likely is a decision to switch to reporting the lower IFCC numbers as percentages. Although some IFCC members had initially pushed for that, the majority have now come to realize that it would just cause too much confusion, Dr. Sacks said.

In addition, there is actually evidence to suggest that lowering the reported A_{1c} values might even worsen diabetes control. A study done in Sweden, where reported A_{1c} values were changed twice during the 1990s, showed that glucose control actually improved by about 0.5% among 49 children and adolescents when the reference scale was raised from an HPLC method with a normal range of 3.0% to 4.6% to the DCCT standard (normal range 4.1%-5.7%) in 1992.

But when the reference was lowered in 1997 to the Swedish national standard (normal range 3.1%-4.6%), the patients' control deteriorated by 0.5% and remained at that level for 2-3 years, despite extensive educational efforts. The findings suggest that "the psychological impact of the absolute numbers is very high when even small changes are made to the patients' reference levels," Dr. Ragnar Hanas of Uddevalla Hospital, in Sweden, concluded (Diabetes Care 2002;25:2110-1).

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DR. SACKS

Noted Dr. Sacks, "At this point, nobody thinks it's a good idea to lower the numbers. … Whatever we do, it will be done in such a way as to not compromise patient care." However, he said, another option being considered is to report the new IFCC values in mmol/L, rather than as a percentage.

Alternatively, the working group could decide that both A_{1c} and mean blood glucose be reported—either permanently or for a transition period—similar to the way laboratories now report both creatinine clearance and estimated glomerular filtration rate based on creatinine. How A_{1c} would be reported in that scenario is also undecided. "It's not clear what will be reported. … All options are still on the table," Dr. Sacks said.

The timetable for all this to happen is similarly hazy. Dr. Kahn believes it could occur as soon as the end of 2007 or early 2008, based on the assumption that the interim data to be presented in June will allow for a good prediction of the final results, while manufacturers have indicated it would take about 6-9 months to change the settings on the instruments.

But Dr. Sacks is more cautious, estimating that it would take at least a year beyond the final study report in September to analyze the results and, if a change is made, to undertake what will need to be a "huge public education effort."

Dr. Kahn believes that a change to mean blood glucose would ultimately benefit patients, many of whom are still unclear as to how something called "hemoglobin A_{1c}," expressed as a small percentage, relates to the daily readings on their blood glucose monitors.

"People are doing meter readings and getting numbers like 130 or 150. … They say, 'What's that got to do with an 8?' It's all very confusing," he said.

Dr. Kahn is already preparing for the public education campaign: "I have a book on how [the European Union] converted to the Euro. That's the best analogy." ■

Feedback Can Improve MDs' Diabetes Care

BY PATRICE WENDLING
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TUCSON, ARIZ. — Providing physicians with semiannual or quarterly feedback on their ability to manage their patients' glycemic control, as reflected by hemoglobin A_{1c} levels, could improve suboptimal diabetes care in primary care settings, Dr. Yar Pye and colleagues reported in a poster at the annual meeting of the North American Primary Care Research Group.

Dr. Pye reported on data from a 30-month observational study in which physicians received feedback regularly with regard to their patients' average hemoglobin A_{1c} values, the percentage of patients with data on HbA_{1c} for the last 6 months, and the percentage of patients with controlled and uncontrolled diabetes. The physicians also were informed about the average HbA_{1c} level for the whole clinic and their peers, Dr. Pye said in an interview. Patients were not given the information.

There were 360 nonpregnant diabetic patients, aged 27-89 years, being seen at the Lutheran Family Medical Center in Brooklyn, N.Y., where Dr. Pye practices. Two-thirds were female; the median age was 61 years.

Performance profiles were sent once in 2004, twice in 2005, and quarterly in 2006 until June 2006. Patients who did not have an HbA_{1c} value for the previous 6 months or who had uncontrolled diabetes, defined as a HbA_{1c} of more than 9.5%, were telephoned by staff or notified by mail for retesting and further treatment.

The average HbA_{1c} level decreased from 8.3% in December 2004 to 7.7% in June 2006, the authors wrote. During the same time period, the percentage of diabetic patients with a known HbA_{1c} increased from 75% to 83%, while the percentage of patients with uncontrolled diabetes decreased from 23% to 16%.

HbA_{1c}, which is not subject to the fluctuations seen with daily blood glucose monitoring, is being used increasingly as a target in glycemic control. In 2006, New York City took an unprecedented step when it mandated that all laboratories report HbA_{1c} test results directly to the New York City Department of Health.

The Canadian Institute for Health Information recently introduced semiannual tracking of HbA_{1c} as one of 105 primary health care indicators, Dr. Pye said. The American Diabetes Association recommends that HbA_{1c} be measured in patients with diabetes at least twice yearly. ■