

Host: This is the podcast from *Clinical Chemistry*. I am Bob Barrett.

Until recently, hemoglobin A<sub>1c</sub> was used only as a key task for monitoring glycemic control in people with diabetes.

More recently, it's been proposed as the preferred test for diagnosis of diabetes, and it's being used by some to calculate an estimated average glucose concentration.

An article published in the January issue of *Clinical Chemistry* reported on the imprecision, bias, and total error of eight point-of-care hemoglobin A<sub>1c</sub> analyzers.

Dr. David Sacks, an Associate Professor of Pathology at Harvard Medical School and Medical Director of Clinical Chemistry at Brigham & Women's Hospital in Boston, continues the discussion as our guest in this podcast.

So tell us, Dr. Sacks, what is the role of hemoglobin A<sub>1c</sub> in monitoring patients with diabetes?

Dr. David Sacks: Hemoglobin A<sub>1c</sub> is formed by the attachment of the glucose molecule to molecule of hemoglobin, and the concentration of hemoglobin A<sub>1c</sub> in the blood, therefore, depend on both the concentration of glucose and the lifespan of the red blood cell. Now because the red blood cells lives for approximately 120 days, the hemoglobin A<sub>1c</sub> value represents the average or integrated, if you will, glucose concentration over the proceeding 8-12 weeks.

So hemoglobin A<sub>1c</sub> is a fundamental component in the care of patients with diabetes that is used to monitor long-term glycemic control, so the control that the patients had over several days, or weeks, or months. It is very important decision-making point in whether the patient's therapy should be adjusted. This is both for patients who take insulin and also for patients who take oral agents without insulin.

The decision whether to give them more therapy or additional therapy is based on the hemoglobin A<sub>1c</sub> concentration. It is also used to assess the quality of diabetes care, particularly in the United States, and payment and reimbursement by some insurance companies is dependent upon the number of patients with diabetes who have low hemoglobin A<sub>1c</sub> concentrations. The other important use is that it is a measure of the risk for the development of complications of diabetes, particularly the microvascular complications or small vessels which result in retinopathy or blindness, nephropathy or kidney disease, and neuropathy, which is nerve damage.

A more recent and still perhaps controversial in some people's minds, use of hemoglobin A<sub>1c</sub> is for the diagnosis of diabetes. So it's quite clear that hemoglobin A<sub>1c</sub> is absolutely essential for all patients who have diabetes.

Host: And how accurate and precise does measurement of hemoglobin A<sub>1c</sub> need to be?

Dr. David Sacks: Well, that's a difficult question to answer. There is actually no consensus as to how accurate it needs to be. I think to sort of get some kind of concept as to this question is to look at the major clinical trials. And there have been two very large perspective clinical studies done in patients with diabetes. One is called the DCCT, or Diabetes Control and Complications Trial, which was done in individuals with type 1 diabetes and this was published in 1993, and the second big study was United Kingdom Prospective Diabetes Study or UKPDS, which enrolled patients with type 2 diabetes and was published in 1998.

Both of these large perspective randomized clinical trials showed that hemoglobin A<sub>1c</sub> was very important in predicting the risk for development of complications. In both studies, they showed the change of 1% of hemoglobin A<sub>1c</sub>. So for example, if your hemoglobin A<sub>1c</sub> goes from 9% to 8%, this corresponds to about a 30 to 35% reduction in the risk of developing microvascular complications. So it's quite clear that a 1% change is very significant. And if one asks a clinician, many clinicians—again, this is not evidence based, by many clinicians will state that a change of 0.5% in hemoglobin A<sub>1c</sub> is clinically significant and that's the change in which they will act to adjust the patient's therapy.

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Host: Well, with that in mind then, just how accurate is measurement of hemoglobin A<sub>1c</sub> and does it differ between laboratories and methods?

Dr. David Sacks: Well, I think one has to look at this in a historical perspective to really understand it. So the assays to measure hemoglobin A<sub>1c</sub> became commercially available in 1978, so that's a long time we ago; it's a little over 30 years ago. And in 2010, they are probably about close to 100 different assays that are commercially available to measure hemoglobin A<sub>1c</sub>.

Now, the vast majority of the ones that are used in actual patient care are either immunoassays, which are antibody-based tests or HPLC, which uses a column, high-performance liquid chromatography. Now, because of this very large number of methods that were originally available, there was a very wide variation of results. For example, if

one looks at the CAP surveys, the College of American Pathologists, I think it's very informative in 1973 that was the year that DCCT was published. A single sample could have been 9% if sent to one laboratory and the same sample if measured in a different laboratory could have been 20%. Now as I mentioned earlier, change of 1% in hemoglobin A<sub>1c</sub> has very significant impact on patient care and the risk for complications.

So clearly, this was an untenable situation. In response to this, the AACC, the American Association for Clinical Chemistry, decided in 1993, the same year, to try to standardize or harmonize hemoglobin A<sub>1c</sub> testing among labs, and this results in a few years later in the formation of the NGSP, or National Glycohemoglobin Standardization Program. The goal or the purpose of the NGSP is to standardize glycosylated hemoglobin test results so that the results in an individual clinical laboratory are comparable to those in the DCCT and the UKPDS.

Well, they are, as I mentioned earlier, the clear relationships to the risk for microvascular complications and the way the NGSP worked is NGSP works with manufacturers to standardize the instruments, and then the second component is the NGSP works with the clinical laboratories to make sure that the laboratory that measures the patients sample will have the same result as it would have been obtained in the DCCT.

This has result in a significant improvement in assay performance among laboratories, and if one looks at the 2010 CAP surveys, almost all the widely used methods have CVs or coefficient of variation between laboratories that's less than 3.5%, and I think that is quite a good goal that one can go for.

Within laboratories, CVs are very low; some methods can be as low as less than 0.5%, and I think a reasonable current target is within-lab CV of less than 2%.

Host: What are the advantages of hemoglobin A<sub>1c</sub> measurement at point-of-care?

Dr. David Sacks: So the point-of-care testing is where a doctor or a nurse in a practice can actually measure the patient's hemoglobin A<sub>1c</sub> and get an immediate result while the patient is there. So it's rapid, and it's very convenient; just a little finger-stick, and the result is available in just a few minutes.

The testing is also waived, so it does not require trained personnel in the United States. There is CLIA which is Clinical Laboratory Improvement Amendments, which

actually waives these tests. So anybody can perform it, and the sample doesn't have to be sent to the central lab.

There is some evidence from several publications and literature that immediate feedback of the hemoglobin A<sub>1c</sub> results improves glycemic control in patients. So for example, if the doctor sees the patient, knows their hemoglobin A<sub>1c</sub>, they can say to them, look your hemoglobin A<sub>1c</sub> is higher than I would like. You need to increase your insulin, or we need to increase the dose of your medication, your oral medication. So it has several practical advantages.

Host: So then what are the disadvantages of hemoglobin A<sub>1c</sub> measurement at point-of-care?

Dr. David Sacks: Well, unfortunately, there are several disadvantages. The one is more expensive than performing it in a central or clinical laboratory and as I mentioned earlier, this is an advantage but I think it's also a disadvantage that the test is waived which means that it does not require proficiency testing so the very limited objective data as to how well the device has performed in actual patient care.

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So for example, I mentioned before that the NGSP works with clinical laboratories who have to participate in proficiency testing. So we know how well these laboratories perform but with point-of-care testing, they don't have to compare themselves to other laboratories. Some of the devices lack accuracy and precision, and there was a paper published in *Clinical Chemistry* earlier this year, which looked at eight commercially available point-of-care devices for hemoglobin A<sub>1c</sub> and found that only two of these devices met the acceptance criterion of the total CV of less than 3% in the clinically relevant range. Only one of these eight devices actually met the current NGSP criteria.

Another important limitation of these point-of-care testing devices that was evident in the study was the devices showed considerable bias. And the bias ranged from -0.9% to +0.4% in the study. Now, bias, as many people know, would indicate if you have a positive bias, for example, if the true hemoglobin A<sub>1c</sub> is 6.5, if the positive bias is 0.4% then the instrument will tell you that that hemoglobin A<sub>1c</sub> is actually 6.9%.

What this would result in, if one used particularly a point-of-care testing device for diagnosing diabetes, the current cutoff recommendation is 6.5%. So if one looks at the distribution of adults in the US population, aged 20 or more, if you take 6.5 as the cutoff, then there would be 2.4 million

people, approximately adults, aged 20 years or greater, in United States who would meet the hemoglobin A<sub>1c</sub> criterion for diagnosis.

If the meter has a positive bias of 0.4%, any person with the hemoglobin A<sub>1c</sub> of 6.1 or greater would then be detected by this meter as having hemoglobin A<sub>1c</sub> of 6.5 or greater. So that would result in 5.4 million adults in the US population. So you would have a more than two-fold increase in the number of people with diabetes, and this obviously has significant and substantial implications. And I think based in part on some of these issues, the American Diabetes Association, who endorsed in January this year the use of hemoglobin A<sub>1c</sub> for diagnosis of diabetes, stated and I quote them "point-of-care A<sub>1c</sub> assays are not sufficiently accurate at this time to use for diagnostic purposes."

So, they specifically excluded the point-of-care devices from the diagnostic criteria or even for screening patients for diabetes or early stages of diabetes, which some people call pre-diabetes. So despite the availability of these point-of-care devices and the availability and the practical application of these, based on the analysis in the published data, very few of these devices actually meet the clinical needs particularly for diagnosis.

Host:

Dr. David Sacks is an Associate Professor of Pathology at Harvard Medical School and the Medical Director of Clinical Chemistry at Brigham & Women's Hospital in Boston. He has been our guest today in this podcast from *Clinical Chemistry*.

I am Bob Barrett. Thanks for listening.

Total Duration: 14 Minutes.