Clinical Chemistry

Reporting Hemoglobin A_{1c}: Do the Units Matter?

Articles:
D. Sacks. *Reporting Hemoglobin A1c: Do the Units Matter?*
Clin Chem 2013;59: 1427-1429.
http://www.clinchem.org/content/59/10/1427.extract

E.S. Kilpatrick, A.S. Rigby, S.L. Atkin, and J.H. Barth. *Glycemic Control in the 12 Months following a Change to SI Hemoglobin A1c Reporting Units.*
Clin Chem 2013;59: 1427-1429.
http://www.clinchem.org/content/59/10/1427.extract

Guests: Dr. David Sacks is Chief of the Clinical Chemistry Service at the National Institutes of Health, Bethesda, Maryland. Dr. Eric Kilpatrick is from the department of Clinical Biochemistry, Hull Royal Infirmary in the UK.

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

Hemoglobin A1C is one of the analytes most commonly measured in clinical laboratories in patients with diabetes mellitus.

Physicians use Hemoglobin A1C to monitor long-term glycemic control, adjust therapy, and predict complications of diabetes. It was recently added as a criterion for diagnosis of diabetes.

However, due to many standardization efforts, many countries have implemented or are considering implementing a change in Hemoglobin A1C units from traditional percentage values to the preferred SI unit of millimoles per mole.

Concern exists that such a large alteration in numeric values might lead through confusion to a deterioration of patients' glycemia.

A recent study by Dr. Eric Kilpatrick published in the October 2013 issue of *Clinical Chemistry* has assessed the effects of such a change in a diabetes population in the United Kingdom. That article was accompanied by an editorial by Dr. David Sacks in the same issue.

Both Dr. Kilpatrick and Dr. Sacks are our guests in today's Podcast. We'll start with you, Dr. Sacks. Tell our listeners a bit about Hemoglobin A1C measurement.

Dr. David Sacks: Well, Hemoglobin A1C is the analyte most commonly measured in clinical laboratories for patients with diabetes. And it's used very widely for several purposes, one is it's used to monitor long-term glycemic control. It's very importantly used to adjust therapy, and it's also a predictor of complications of diabetes. Finally it was recently added as a criterion for the diagnosis of diabetes.

Now Hemoglobin A1C is formed by the non enzymatic attachment of glucose to the N-Terminal Valine Residue on the beta chain of hemoglobin and this process is termed glycation.

The first documented increase of Hemoglobin A1C in the blood of patients with diabetes was made by Sam Rahbar in 1969.

The problem that arose with patient care was that the early commercial assays that were developed to measure Hemoglobin A1C were not standardized. So the results varied considerably, depending on which assay.

For example, a study published in *Clinical Chemistry* journal in 1992 compared seven methods and found that the results for a single sample varied from 4% to 8.1% among the different methods.

Bob Barrett: Well, doctor, how was the problem with standardization addressed?

Dr. David Sacks: The impetus for standardization was the publication in 1993 of the DCCT, or the Diabetes Control and Complications Trial.

This study randomized 1,441 patients, all of them had Type I diabetes, to either intensive or conventional insulin therapy. They all needed insulin because they had Type I diabetes.

And it was shown that the patients in the intensively treated group had improved glycemic control and this was validated by them having a mean Hemoglobin A1C value of 7% which was significantly lower than the conventionally treated group who had a Hemoglobin A1C of 9.2%.

Now the importance of Hemoglobin A1C was dramatically shown in the study because a small change of Hemoglobin A1C, for example from 9% to 8%, was associated with a very large reduction in the risk of micro-vascular complications. For example, retinopathy, which affects the blood vessels in the eye, was reduced by over 30% by this 1% change in Hemoglobin A1C.

So it became very clear from the study that the Hemoglobin A1C assay needed to be improved.

Three countries—Japan, Sweden and the United States—established standardization programs very shortly after the DCCT was published.

The NGSP which used to be called the National Glyco Hemoglobin Standardization Program was formed in the U.S. and this became the most widely adopted standardization program in the world.

The NGSP has a network of laboratories that works with manufacturers of Hemoglobin A1C assays to assist them in calibrating their methods so that the patients' values correlate with those of the DCCT.

Bob Barrett: Doctor, describe the approach that was taken by the International Federation for Clinical Chemistry and Laboratory Medicine?

Dr. David Sacks: In contrast to the other approaches for standardization, the IFCC, International Federation for Clinical Chemistry and Laboratory Medicine, developed a higher order reference method for Hemoglobin A1C.

And this was achieved by a combination of High Performance Liquid Chromatography, HPLC, and mass spectrometry or capillary electrophoresis. And the IFCC method is designed to be the most accurate method for measuring Hemoglobin A1C.

Bob Barrett: What happened when the standardization methods were compared?

Dr. David Sacks: So that's a very important finding. The methods were compared between the IFCC and the other standardization schemes, and it was noted that the IFCC values were lower than those of the NGSP and the other standardization schemes.

The NGSP values were approximately 1.5% to 2% higher than the IFCC values. There was a linear relationship and a master equation was developed to switch between the two methods to convert the values between IFCC numbers and NGSP numbers, but the values were not the same.

Bob Barrett: How was Hemoglobin A1C reported?

Dr. David Sacks: So historically, Hemoglobin A1C has been reported as a percentage, that is the fraction of the total hemoglobin in the blood that is Hemoglobin A1C.

In healthy individuals the Hemoglobin A1C ranges from about 4% to perhaps 5.5%. And the NGSP reports in percentage which was the units used in the DCCT study and subsequently in a study called the UKPDS, United Kingdom Perspective Diabetes Study, which was directed towards patients with Type II diabetes and showed that lowering

Hemoglobin A1C in these patients reduced their complications.

The NGSP and percentage, DCCT percentage, reporting is used exclusively in United States, Canada, and Japan.

Now the IFCC decided to use SI units to report IFCC methods, and the SI units chosen were millimoles of Hemoglobin A1C per mole of hemoglobin.

So for example, a Hemoglobin A1C value of 6.5% is equivalent to 48 millimoles per mole. It's clear that these large differences in the numbers would eliminate confusion about the reporting scheme.

The SI units are used exclusively in several countries including Australia, New Zealand and parts of Europe such as Germany, Italy and of course the United Kingdom, which forms the basis for Dr. Kilpatrick's studies.

Bob Barrett: Well, let's talk about Dr. Kilpatrick's studies with Dr. Kilpatrick. Doctor, why did you carry out this work?

Dr. Eric Kilpatrick: Well, Dr. Sacks has just described how the IFCC standardization initiative proposed not only a change to the values of Hemoglobin A1C, but also change to the unit so that instead of reporting them as a percentage Hemoglobin A1C, they were now to be reported as millimoles per mole.

And as he described, that's made a huge difference to the numbers that we are likely to report. And they were concerns when these new units were about to be adopted that such a large change in the numbers reported might lead, through confusion more than anything else, to a subsequent deterioration in the glycemia of patients.

Now in the UK, we had an opportunity to test this because we were changing over units and in 2009, we started reporting Hemoglobin A1C in both the NGSP, that's a percentage unit, and the IFCC or the SI units, that's the millimoles per mole, so-called "dual reporting." So the report had both these numbers on the same report and we could then request that the test, could refer to one or the other and hopefully be able to get more accustomed to the newer numbers.

Now after just over two years of this dual reporting, the moment of truth really came when we removed the NGSP result and just reported Hemoglobin A1C as millimoles per mole.

What we did in this study was to look at the Hemoglobin A1Cs of diabetes patients in our area of the UK before and

after the unit change, to see if there was any difference after the NGST result was removed.

Bob Barrett: Well, doctor, what were your main findings?

Dr. Eric Kilpatrick: We compared the Hemoglobin A1Cs of over 13,000 patients in the twelve months before the unit change with the values in the same patients in the twelve months after the change and actually found there was no difference in their overall glycemic control of the population from one year the next.

We then looked to see if the response of a high Hemoglobin A1C or the response to a high Hemoglobin A1C result was any different depending on whether the result shown included the familiar NGSP results or not.

When we looked at the 4,000 or so patients with a Hemoglobin A1C greater than 8% or in new units that would be 64 millimole per mole, the next Hemoglobin A1C result in the same patient fell on average by the same amount, whether or not the initial result was an NGSP percentage result or just an SI millimole per mole result.

And so overall our work was suggesting that in our UK population a move to SI units for Hemoglobin A1C doesn't lead to any marked short-term deterioration in the glycemic control of these patients, or that there was any different Hemoglobin A1C outcome in patients who were initially, purely controlled.

Bob Barrett: Were there any limitations to your work?

Dr. Eric Kilpatrick: Well, I suppose there is always limitations to any study, and one of ours certainly was that the data was collected just over a twelve-month period. And so perhaps that wasn't long enough to identify true long-term changes that might be associated with the change in reporting units.

Also, the only data we collected was Hemoglobin A1C data. So we weren't able to include other aspects of the patients' diabetes such as the type of diabetes they had, the duration of diabetes, or the treatments they were receiving.

Bob Barrett: Dr. Sacks, given your editorial, do you have anything to add to that?

Dr. David Sacks: Yes, I'd just like to comment by first saying that I think that Dr. Kilpatrick's study is a very valuable contribution to patient care in terms of the potential problems with switching units, and he has discussed some of the limitations.

Some other limitations include the breakdown of patients with Type I versus Type II diabetes. Some pediatricians who treat children with Type I diabetes believe that there may be differences in pediatric populations versus adult populations in terms of the understanding of Hemoglobin A1C.

Another question that arises is whether there was any difference between the patients who are managed by diabetologists versus those treated by general practitioners.

And another question is whether any physicians or patients may have obtained the percentage, the NGSP values, in addition to the SI units which were the only units on the printed reports and if this was done, did this influence the patients?

I think one other important issue that has been debated quite widely that Dr. Kilpatrick's study sort of shed some light on with the limitations that he has described is that a lot of effort was put into this, and the UK is a wealthy country and a lot of education was done. Can these findings be extrapolated to other countries? I think it remains to be seen when studies are published from other countries whether the results will be the same as those shown by Dr. Kilpatrick.

Dr. Eric Kilpatrick: I think these are all very valid comments that have been made by Dr. Sacks. We did have a very good educational material here that went to both healthcare and laboratory professionals and also it went to the patients themselves.

So I think during that period, especially during the two years when we had dual reporting, there was an awful lot of information went out there and we might also have underestimated the ability of healthcare staff to adopt to these new numbers. We assumed they would have a difficult time, may be it was actually easier that than we had anticipated.

And lastly, and this was touched on by Dr. Sacks, it's possible that they just found an ingenious way to convert the new numbers back to the old ones and they are still were actually using these old numbers to some extent at least.

Bob Barrett: Let's look ahead, Dr. Kilpatrick, what more work needs to be done?

Dr. Eric Kilpatrick: Well, one of the limitations we had was that there was such a short period of follow-up and I think it troubles us at least and probably other people that were repeating the study to see if there are any longer term changes in glycemia due to the unit change.

And I think it would be helpful for other centers to do similar work and in different countries to see if whether our findings can be confirmed by other people or not as the case may be.

Bob Barrett: And Dr. Sacks, overall, what are the implications of Dr. Kilpatrick's study?

Dr. David Sacks: Well, I think Dr. Kilpatrick's study was very well designed and can serve as a template for other the countries that plan to convert from NGSP to SI units.

I think it's vital that this be done in a very organized fashion with adequate education to both patients and healthcare professionals.

And, I think the other important thing that was done was in the UK, all the laboratories converted the units on the same day, which minimized the potential for confusion that could arise if some laboratories are reporting one set of units and other laboratories reporting another.

I think the ultimate question that has to be borne in mind is whether converting the units will jeopardize the health of patients, and I think for countries that are considering changing units, I think it's absolutely vital that they avoid jeopardizing the health of patients by performing this process.

Bob Barrett: Dr. David Sacks is Chief of the Clinical Chemistry Service at the National Institutes of Health, Bethesda, Maryland. Dr. Eric Kilpatrick is from the department of Clinical Biochemistry, Hull Royal Infirmary in the UK.

They've both been our guests in this podcast from *Clinical Chemistry* on Hemoglobin A1C.

I am Bob Barrett. Thanks for listening.