

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

Hemoglobin A1c measurements are key for monitoring glycemic control and diabetes and they are used to trigger adjustments and behavior in treatment. However, evidence suggests that patients and perhaps some clinicians may have difficulty in relating Hemoglobin A1c measurements to those of blood glucose.

The April issue of *Clinical Chemistry* published a point and counterpoint on whether converting hemoglobin A1c to so-called "estimated average glucose" is scientifically justified and whether it is likely to be helpful in practice.

Dr. David Sacks is co-author of the Point and is an Associate Professor of Pathology at Harvard Medical School and the Medical Director of Clinical Chemistry at Brigham and Women's Hospital in Boston.

Dr. Ian Young is author of the Counterpoint and is a Professor of Medicine and Director of the Center for Public Health at Queens University, Belfast. They are both our guests in this podcast.

So tell us, Dr. Sacks, how exactly is the efficacy of therapy for diabetes evaluated?

Dr. David Sacks: Well, there are two techniques that are used by healthcare providers and patients. The first one of these involves self-monitoring of blood glucose by patients themselves who use portable meters and there are also some patients, relatively small number, use continuous blood glucose monitors or sensing devices.

And patients use these to make daily decisions regarding medication doses, and/or to modify food intake. And that is a very important aspect of these meters particularly in patients who use insulin as to detect hypoglycemia or low blood glucose because patients who have hypoglycemia can actually lose consciousness and unable to treat themselves.

Now the second strategy is measurement of glycosylated hemoglobin or hemoglobin A1c and this provides a more accurate assessment of long-term glucose control than that provided by self-monitoring. So the concentration of hemoglobin A1c which consists of glucose attached to the  $\beta$  chain of the hemoglobin molecule is readily stable. And the mean lifespan of the red blood cell is approximately 120 days, and in any individual, with the normal red cell lifespan, the hemoglobin A1c value reflects the integrated to every glucose concentration over the preceding 8 to 12 weeks.

So hemoglobin A1c is used to assess whether the patient's glycemic target has been reached and whether it has been maintained.

Another important use for hemoglobin A1c is that it predicts the progression of many of the complications of diabetes particularly the microvascular complications, or small vessel disease complications which produce the retinopathy or blindness in diabetes, neuropathy kidney disease which results in many patients requiring dialysis and neuropathy or nerve damage.

Host: With that in mind, what are the limitations of measures of glucose control?

Dr. David Sacks: Separate these into the self-monitoring and hemoglobin A1c. Let's start with self-monitoring first. When the patient measures their glucose with the glucose meter, they are looking at a single point in time, and glucose fluctuates very widely. This depends on the intake of food, the amount of exercise that the person is involved in, and whether there's stress, and so it can change over as shorter time as minutes.

So values obtained by the self-monitoring does not give any indication of what the glucose was an hour before or an hour after this is measured. So the information that it provides is only at the time the blood was sampled.

Another important issue is that the meters tend to have larger imprecision and are less accurate than the instruments used in clinical laboratories. This is because the meters are obviously designed to be small and portable, can be fit easily into somebody's coat pocket or to lady's handbag. They use small sample volumes. So finger prick is fine enough for that and they are also very rapid giving the results in matter of 15 to 20 seconds, some of them.

The other limitation of these meters of course is that there can be errors by the actual user because most of the users are not trained laboratory technologists.

Another limitation is that it's difficult to obtain adequate reliable data from patient's logbooks, patients are asked by physicians to actually note the glucose values every time they do a fingerstick. Some patients don't do it, other patients tend to cheat just a little bit, may be not a little bit. There are other barriers too to implementation of self-monitoring glucose. People don't like sticking their fingers. They ask to do this three or four times a day. It can become quite expensive and some patients complain that they don't

have enough time to do it, and it's very inconvenient. So there are several limitations to the self-monitoring.

For hemoglobin A1c, which is done every three to six months, in patients with stable glucose control, hemoglobin A1c is recommended every six months. In patients where control is not stabilized, the therapy is changed, the recommendation is that it should be measured every three months. Obviously, it's giving you an integrate to do average glucose, one of the big problems however, of hemoglobin A1c is it's very difficult for patients, particularly lay people, to understand why you are measuring hemoglobin, what does hemoglobin have to do with diabetes.

Doctor, I thought diabetes was a disease of sugar and why are you measuring my hemoglobin? I remember when I was pregnant, they measured my hemoglobin because they were worried I had anemia, but what does hemoglobin have to do with diabetes?

So there tends to be a limitation to the understanding of hemoglobin A1c.

Host: Now what is estimated average glucose concentration?

Dr. David Sacks: The estimated average glucose is derived from the hemoglobin A1c value and reflects the average glucose over a period of time like the hemoglobin A1c. The values for estimated average glucose or eAG were derived from a study called the ADAG Study, or A1c Derived Average Glucose Study, that look at patients in different countries: United States, Europe, Africa, and tried to accurately determine the average glucose over a period of three months and compare that to the hemoglobin A1c measurement.

Now due to standardization efforts that have taken place over the last several years, we can measure hemoglobin A1c accurately. It's much more difficult to accurately measure average glucose. The study that was conducted to determine average glucose was performed on healthy individuals, individuals with Type 1 diabetes and individuals with Type 2 diabetes, and the average glucose was estimated from both the patients measuring their glucose using meters at different times of the day. So some participants did this eight times a day, including waking up in the early hours of the morning to measure their glucose. This was a particularly important time because this tends to be when the glucose concentration is lowest.

In addition, the patients had for 48 hours every month for the three months of the study, they wore continuously

glucose monitor that measures glucose subcutaneously every few seconds and so on average each participant in the study had about 2,700 glucose measurements performed over the three months of the study.

So because of the large number of glucose measurements we could come as close as, is feasible with current technology to obtaining the average glucose in those individuals over three months. And analysis by statisticians of the hemoglobin A1c, and the average glucose revealed a strong linear relationship between average glucose and hemoglobin A1c. And the study provided a simple linear regression equation that allows hemoglobin A1c values to be converted to average glucose.

Host: How does estimated average glucose concentration relate to other measures of glucose control?

Dr. David Sacks: Well, to facilitate communication with patients, many healthcare professionals translate hemoglobin A1c values into the average plasma glucose. The tables exist that converts A1c to average glucose. These are available in print, for example, clinical practice recommendations that are published by the American Diabetes Association. They are available on websites, in hospitals, you can see them in pasted up on the wall sometimes, in doctors' offices, and very frequently, particularly in the United States, in the lab coat pocket of members of the diabetes healthcare team.

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So, it's important to realize that the values of these estimated average glucose is not the same as a fasting glucose or pre-meal or post-meal glucose result that's obtained by the patient from a finger-stick, that includes all the glucose values over a period of several weeks to possibly even a few months. So again, it represents the integrated glucose that is derived from the hemoglobin A1c.

Host: So then, what's the role of estimated average glucose concentration in patients with diabetes?

Dr. David Sacks: Many clinicians have done studies and have observed that only 25 to 35% of patients with diabetes actually know the hemoglobin A1c values. And it's clear that patient's understanding of the glucose targets and agreeing with therapy changes are critical to long-term success.

Diabetes is more than most other diseases requires constant vigilance by the patients, and the patient has to buy into the whole treatment regimen, and unless the patients actively participate in their own treatment the treatment tends to be

less successful. So it's very important for the patients to understand exactly what they are doing.

Probably the best publication that is looked at communicating hemoglobin A1c results as average glucose to patients was performed in the United Kingdom and published in 2008, and they had 111 patients, some with Type 1 diabetes and some with Type 2, who attended a hospital diabetes clinic.

These patients were provided with information relating to the association between hemoglobin A1c and average glucose. And at the end of the approximately seven months study, patients who had poorly controlled diabetes showed a significant reduction in the hemoglobin A1c values, particularly if they were unfamiliar with hemoglobin A1c at the initiation of the study.

And the magnitude of improvement in glycemic control was greatest in those patients with the most poorly controlled diabetes.

So these data underscore how critical it is for patients to be educated about hemoglobin A1c and average glucose and the understanding of these data needs to be assessed because average glucose can be a powerful tool to improve glycemic control.

Now not everyone will use estimated average glucose. It's beneficial in the management of patients with diabetes, and the recommendation is that clinical laboratories should report an estimated average glucose along with the hemoglobin A1c to those individuals who find this information useful in guiding diabetes management.

So those clinicians, diabetes educators, nurses who find communication with their patients improved by explaining the average glucose concept to their patient, they should be provided with both the hemoglobin A1c value and the eAG value and then they can communicate with their patients and help the patients understand.

It's interesting that the most enthusiastic supporters of eAG or diabetes educators who are the healthcare professionals who tend to spend the most time interacting with patients.

It is also essential that laboratories use the correct formula to calculate eAG. There is an old formula that was based on a retrospective examination of data from the DCCT, but that's not the correct formula. The correct formula is the one that's based on the ADAG study. This is now available on the ADA website, it's on the NGSP website, and education efforts are ongoing to make sure that

laboratories, which tend to use the information technology to report at an estimated average glucose with the Hemoglobin A1c use the correct equation.

Finally, I just like to emphasize that it's very important to clinical laboratorians to communicate with clinicians, diabetes educators, and other healthcare providers to enhance the care of patients with diabetes.

Host: Now, Dr. Young, you don't agree with Dr. Sacks about the reporting of hemoglobin A1c as estimated average glucose. What are your main objections?

Dr. Ian Young: Well, I guess first of all, I should quantify well, I do agree with Dr Sacks and that is, that it's really important for patients to understand what their HbA1c result means. However, I certainly don't agree with him that this will be most successfully achieved by using estimated average glucose. And I think I probably have three main objections to the use of eAG.

If eAG as a concept is going to work, then there has to be a reliable and consistent relationship between the HbA1c result and the patient's average glucose.

In fact, I think that when you look at the relationship in individual patients between estimated average glucose and HbA1c, then you come up with a number of different relationships in different individuals.

Where this is most marked, I think if you look at different ethnic groups, there is a wealth of evidence to show that in ethnic groups, if the true average glucose is the same, in fact the HbA1c will differ according to the ethnicity of the individual.

This is maybe a little bit surprising at first thought, but it is, due to the fact that the relationship between glucose levels and glycation of hemoglobin is a complex one. It is determined not only by a simple chemical reaction between glucose and the Hemoglobin molecule, but also by a series of enzyme-mediated reactions, which remove glycated residues from the Hemoglobin molecule, and this process of de-glycation seemed to be under quite significant genetic control and vary between individuals.

So this means that between different individuals that can easily be a 1% difference in HbA1c levels, despite the fact that they run the same level of glucose.

Apart from those genetic factors, which result in different degrees of glycation in different individuals, then the extent

to which HbA1c varies depends on red cell turnover, not something which is much more widely understood.

So individuals with renal failure or hemoglobin variants and/or anemia due to iron deficiency or B12, or folate deficiency, or some other cause, or in pregnancy will have different degrees of red cell turnover. This will mean that the relationship between glucose and HbA1c is different, and that at any constant glucose level the HbA1c may differ by as much as a couple of percent.

So in other words, glycation and de-glycation of hemoglobin vary between individuals at fixed glucose levels. I think that's important consequences when it comes to translating an HbA1c into an average glucose.

If we use a simple equation, which is what is proposed at the moment then every individual within HbA1c I'll say 6.5% is given the same estimated average glucose result. When in reality the true glucose levels of those individuals may be quite different.

So I think that the use of estimated average glucose is potentially misleading and really quite fundamentally flawed.

Host: Now what about the ADAG study? Now, surely that must provide some evidence where reporting is estimated average glucose.

Dr. Ian Young: Well, ADAG Study, or the HbA1c Derived Average Glucose Study, is certainly one of the best studies, which is being done to date, which is thought to look at the relationship between HbA1c and glucose levels. However, I think there are a number of limitations around the ADAG study.

First of all, it only required 90% of individuals to be within 15% of the estimated average glucose value, and derived from the regression line relating glucose concentration to HbA1c. Just about to achieve that criterion what that means is that 10% of the individuals in the study had true levels of glucose more than 15% away from the estimated average value.

If we think about what that figure means, then for 10% of individuals, and it was possible to have as much as a 35% difference between the true main glucose, despite the fact that they would be assigned same estimated average glucose concentration.

So in other words, while we derive an equation which gives a sense of certainty about translating HbA1c to glucose from the ADAG study, that equation is really rather misleading.

The reality of it is that rather than a single fixed value, it means that 95% of individuals have as much as a 44% difference in the glucose. So that's one area with the ADAG study. I think it's potentially misleading, but in addition although it's been the largest and best study done to date, it included only 700 individuals, of whom 300 of Type 1 diabetes, 300 Type 2, and a 100 healthy volunteers.

The vast majority were Caucasian, numbers and other ethnic groups were small, and there was nobody there with renal failure and/or pregnancy, or variant hemoglobins or the other important illnesses, which we know can affect HbA1c, and children were excluded.

In other words, there are a lot of patients with diabetes, for whom the ADAG equations simply may not be valid, because the study population was so restricted.

Host: Now, hemoglobin A1c is a difficult concept for some patients to understand, while estimated average glucose seems a little simpler to get. Surely a change in reporting may help patients to more easily understand the results.

Dr. Ian Young: I think the idea that patients understand estimated average glucose more easily than HbA1c, is an attractive one when presented in those terms. I think the argument is that, patients monitor their glucose, and therefore are used to thinking about glucose values because they see them frequently on their glucometers.

Suddenly when a patient goes to a physician, and they check how their diabetes is controlled, suddenly seemingly out of nowhere comes this parameter HbA1c, which is one that seems foreign and strange and far away from patient's everyday experience.

So, I do understand the attractiveness of being able to convert an HbA1c to something that reflects average glucose for patients, and that's the argument, but again, I think there are problems when you begin to prove it. And firstly, I think there are many patients with diabetes who don't in fact monitor their own glucose, particularly patients with Type 2 diabetes, and therefore average glucose is just as meaningless to them as HbA1c unless they say receive good education.

But possibly more of a problem than that is the fact that whenever a patient does measure their own glucose with their glucometer, many of their machines will report for them, the average glucose value for last 20 or so measurements that they have taken. So a patient can press a button on their glucometer and get an average glucose.

That average glucose that the patient gets is very different from the estimated average glucose, which would be produced through applying an equation to the HbA1c result. And a conversation with the patient which seeks to explain that the average glucose on the machine is not the same as the estimated average glucose, and to explain why there are differences between the two, that's potentially very difficult in educational terms.

In fact, patients are going to notice that the average glucose from their machine is very different than the estimated average glucose from the laboratory and that may cause them to question why the difference exists and maybe even to think that the laboratory result is inaccurate and that there are problems in the laboratory.

So, I think estimated average glucose, while it is superficially attractive, is actually quite a difficult concept, and there has been at least one good randomized trial that you show them that what matters with patients, it's not whether you talk about estimated average glucose or HbA1c, but the quality of the education, which is what the patient has been given and the help that's been provided to enable them to understand the meaning of the result.

Host:

Dr. David Sacks is an Associate Professor of Pathology at Harvard Medical School and the Medical Director of Clinical Chemistry at Brigham and Women's Hospital in Boston.

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Total Duration: 25 Minutes