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M. Sue Kirkman and David B. Sacks.
Glycated Albumin: Added Value or Redundancy in Diabetes Care?
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Guest: Dr. David Sacks from the Clinical Chemistry Service Department of Laboratory Medicine at the National Institutes of Health in Bethesda, Maryland.

Bob Barrett: This is a podcast from *Clinical Chemistry,* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I'm Bob Barrett. Fasting plasma glucose and glycated hemoglobin are the standard measures used to screen and diagnose diabetes but both have limitations. Plasma glucose requires an overnight fast and has high within person variability, while hemoglobin A_{1C} is unreliable in certain patients, including those with altered red blood cell turnover, anemia, some hemoglobinopathies, or chronic kidney disease. Another potential marker is glycated albumin, which is formed when glucose binds to albumin and reflects intermediate hyperglycemia.

Two papers appearing in the March 2022 issue of *Clinical Chemistry* examined the role of glycated albumin for the diagnosis of diabetes and the risk of mortality in the U.S. adult population. Those papers were the subject of an editorial in that same issue, by Dr. David Sacks, a Senior Investigator and Chief of the Clinical Chemistry Service Department of Laboratory Medicine at the National Institutes of Health in Bethesda, Maryland. And we are pleased to welcome back Dr. Sacks to our podcast.

First of all, doctor, what exactly is glycated albumin?

David Sacks: Well, glycation is the non-enzymatic attachment of glucose to minor groups of proteins. Any protein in the body can be glycated and probably most of them are. And glycated albumin is specifically albumin with glucose attached where an albumin is attaches to lysine residue. And it's important to realize that the circulating half-life of albumin in the blood is somewhere between 14 and 20 days. So, the concentration of glycated albumin reflects the average glucose over the preceding two to three weeks. And so you can imagine that if the glucose is higher, as occurs for example in diabetes, the glycated albumin would be higher.

Bob Barrett: And how does that differ from fructosamine?

David Sacks: Fructosamine is the generic name for all plasma protein ketoamines. Because this includes all glycated serum proteins, it also includes albumin and albumin is the most predominant protein in the plasma, making up about 50% to

60% of all serum proteins. So you can think of glycated albumin as a fraction of the fructosamine.

Bob Barrett: Okay. Well, how does that all differ from hemoglobin A_{1C}?

David Sacks: Hemoglobin A_{1C} is the most widely used marker of average glucose in patients with diabetes. And what hemoglobin A_{1C} is hemoglobin with glucose attached to the N-terminal valine of the beta chain. And the concentration of hemoglobin A_{1C} in the blood depends on two things, it depends on the average concentration of glucose and it depends on the lifespan of the red blood cell, which averages about 120 days. So, based on this, the hemoglobin A_{1C} represents the average glucose over the preceding 8 to 12 weeks. And as I mentioned, it's the cornerstone of management of patients with diabetes. Hemoglobin A_{1C} is used to diagnose diabetes, to monitor the patient's response to therapy, and importantly, to predict the complications of diabetes. And clinicians actually use the hemoglobin A_{1C} to adjust treatment. They target hemoglobin A_{1C} values that they try to obtain to know that the management of the patient is good.

Bob Barrett: Considering the new data published by the Baltimore Group in the March 2022 issue of *Clinical Chemistry*, what in your view is the clinical value of glycated albumin?

David Sacks: So, before I get on to the two papers published by Liz Selvin's group, I just want to mention that glycated albumin is independent of red cells. So, because of this, it can be used in conditions where abnormalities in red blood cell lifespan or hemoglobin variants compromise the use of hemoglobin A_{1C}. For example, certain abnormal hemoglobins or people with sickle cell anemia. Hemoglobin A_{1C} is very limited in its use in these individuals if they have diabetes.

So, the two papers from the Baltimore group, Liz Selvin's group, there were two studies. The first study evaluated glycated albumin for the diagnosis of diabetes and the second one examined the association of glycated albumin with mortality. And both studies used data from the 1999 to 2004 NHANES Survey. Now, the NHANES, or it's abbreviation for National Health and Nutrition Examination Survey, which is a national representative cohort of adults in the United States and it's used very widely to provide estimates of diabetes, both diagnoses and undiagnosed.

So, the first study where they had closed to 5,000 adults from NHANES, they showed that glycated albumin is excellent for detecting undiagnosed diabetes. For example, they found that the area under the ROC or receiver operating characteristic curve was very high. It was 0.82 to .95, depending on whether the diabetes was diagnosed by fasting glucose or by hemoglobin A_{1C}. The sensitivity was not that

good. It was low to moderate in the study, but the specificity was excellent. It was 0.98 or greater, which is excellent for any diagnostic marker.

The other study was larger. They had about 13,000 participants and they followed them for several years after the survey. And they observed that increased glycated albumin was associated with increased mortality in these individuals. And this was especially noticeable in those people who had diabetes. And interestingly, the association was as strong as that of hemoglobin $A_{1C,}$ which has sort of been very widely used for many, many years as the gold standard to predict, as I mentioned, complications and mortality in people with diabetes. And based on their data, both studies concluded essentially with the same information, same conclusion. They thought that glycated albumin is useful as an alternative assay of glycemia.

Bob Barrett: Dr. Sacks, the tile of your editorial asked the question: glycated albumin--added value or redundancy in diabetes care? So, which is it? And what do you hope readers take away from reading your editorial?

David Sacks: So, let me first mention that glycated albumin is expressed as a percentage of total albumin. This is analogous to hemoglobin $A_{1C,}$ which is expressed where the glycated hemoglobin is expressed as a percent of the total hemoglobin. And the glycated albumin is – the advantages I've mentioned a few minutes ago based on the study, the sum of the disadvantages are that it is influenced by changes in the albumin in the blood. And for example, this is important because albumin might be low in end-stage kidney disease, which is a very common, in fact one of the most debilitating and severe complications of diabetes. So, it may be limited in particularly those people where you need to use it.

Another limitation is that the assay is not standardized and different assays, depending on which company the assay is bought from, and the method of analysis, the values will be considerably different even on the same blood sample.

Another limitation is that there are no accepted cut-offs and the one study from Baltimore, the one on the diagnosis, they used a cut-off for diagnosis of 16.5% and 17.8% to identify and diagnose diabetes depending on whether the diabetes was diagnosed with glucose or hemoglobin A_{1C}. So, the cut-offs were 16.5% or 17.8%. In a paper the same group published in 2018, they identified the diagnostic thresholds as 15% or 15.6% and this was with the same assay. They used the same assay in both publications. So clearly, a specific threshold has to be decided upon so that everybody comes to the same conclusion regarding diagnosis. And analogous to the limitation of diagnostic thresholds, there is

no agreed target threshold for treatment. As I mentioned, the hemoglobin A_{1C} is a specific target, generally 7% in most people with diabetes, where the clinicians aim for, and if the patient's hemoglobin A_{1C} is below 7%, they say that's adequate control. This is lacking for glycated albumin, there's no agreed threshold.

Bob Barrett: Well, finally Dr. Sacks what, if anything, can be done about these limitations?

David Sacks: Well, there are a few things – two main things that need to be done. The first is standardization. It's really important that regardless of which lab a patient's glycated albumin is measured in, the result should be exactly the same. An analogous situation existed for hemoglobin A_{1C} 30 years ago and this was remedied by a very large standardization process to make sure that all the values were the same. This hemoglobin A_{1C} standardization was initially performed by the NGSP. And succeeded in really reducing the variation in different assays. So, this is a long-term large project and my understanding is that this has been initiated in Japan already.

The second limitation is that large clinical studies need to be done. So for example, the decision to use hemoglobin A_{1C} was based upon a very large study called the DCCT, Diabetes Control and Complications Trial, for people with type 1 diabetes and then there was another trial called UKPDS for individuals with type 2 diabetes and this resulted in the thresholds that have been selected. So, ongoing studies need to be performed with glycated albumin to clearly identify the clinical value of glycated albumin and, importantly, its role in both the diagnosis and treatment of people with diabetes.

Bob Barrett: That was Dr. David Sacks, a Senior Investigator from the Department of Laboratory Medicine at the National Institutes of Health in Bethesda, Maryland. He has been our guest in this podcast on the role of glycated albumin and diabetes. His editorial, as well as two original scientific papers examining glycated albumin, appear on the March 2022 issue of *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.