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High Glycated Albumin and Mortality in Persons with Diabetes Mellitus on Hemodialysis

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Guest: Dr. Anders Berg is Assistant Director of Clinical Chemistry at Beth Israel Deaconess Medical Center in Boston and Assistant Professor of Pathology at Harvard Medical School.

Bob Barrett: This is a podcast form *Clinical Chemistry* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I'm Bob Barrett.

People with diabetes mellitus experience chronically elevated blood sugar concentrations. And as a consequence of this, suffer from long-term complications such as kidney disease, loss of vision, and increased risk of cardiovascular disease and death. Patients may reduce risk by maintaining normal blood glucose concentrations called glycemic control. This is achieved through changes in diet, exercise, insulin therapy, and other blood glucose lowering medications.

Glycemic control is a lifelong goal and can be a daily struggle for the many people who live with this disease. The most common test used by healthcare providers for monitoring average blood glucose concentrations is hemoglobin A1c, which measures the amount of glycated hemoglobin. There is growing evidence that hemoglobin A1c testing may not be as reliable in patients with diabetic kidney disease. Measurement of glycated albumin may be an alternative to glycated hemoglobin in these cases.

In the February 2017 issue of *Clinical Chemistry*, a paper examines the association between glycated albumin and risk of death in patients with the diabetes mellitus and end-stage kidney disease who are on hemodialysis. The lead author of that paper is Dr. Anders Berg, Assistant Director of Clinical Chemistry at Beth Israel Deaconess Medical Center in Boston and Assistant Professor of Pathology at Harvard Medical School and he joins us in this podcast. So, Dr. Berg, tell us why you were interested in investigating this glycated albumin test, specifically in patients with kidney disease.

Dr. Anders Berg: The importance of hemoglobin A1c testing, both for screening patients for diabetes mellitus and for therapeutic monitoring of patients who already have diabetes mellitus, is something that is well-established. What is perhaps not as well-known is the evidence that hemoglobin A1c testing may not be as reliable in patients with diabetic kidney disease, especially patients on hemodialysis.

The reason for this is because of the high prevalence of anemia in patients with a chronic kidney disease and because of the effects of anemia on hemoglobin A1c values.

Previously, there have been three smaller studies demonstrating an association between glycated albumin and mortality in patients on hemodialysis. However the evidence to date has not resulted with any consensus recommendations for use of glycated albumin in this patient population. Indeed it was the lack of sufficient evidence and potential to improve care that generated our original interest in the present study.

Bob Barrett: Let's go back and have you talk a little more about glycated albumin and why it may be a reasonable alternative to hemoglobin A1c?

Dr. Anders Berg: Blood tests for glycated albumin and glycated hemoglobin have both been previously shown to be strongly correlated with recent average blood glucose concentrations. The difference between the two tests is that hemoglobin has a longer half-life than albumin. And as a result, tests for hemoglobin A1c represent blood glucose concentrations averaged over longer time span. This is one of the reasons that hemoglobin A1c tests are generally favored in most patients with diabetes mellitus. However, in patients with anemias and abnormal red blood cell dynamics, glycated albumin may be a more reliable indicator of time averaged blood glucose concentrations.

In fact, five previous clinical studies found the glycated albumin values were more strongly correlated to average glucose concentration compared to hemoglobin A1c values in patients on hemodialysis.

Bob Barrett: While your study focused on patients with diabetes mellitus who were being treated with hemodialysis, why did you focus on this subset of patients with kidney disease?

Dr. Anders Berg: Patients with end-stage kidney disease on hemodialysis were at the highest risk of anemia. These patients often require erythropoietin or other erythropoietin stimulating agents. After each injection of erythropoietin, patients experience sudden increases in red blood cell production and a sudden increase in red cell production introduces new hemoglobin into the circulation, which is completely unglycated causing a sudden decrease in hemoglobin A1c values.

Similarly, after the effects of erythropoietin wear off, erythropoiesis stops and the patient's erythrocytes become progressively older with no new erythrocytes being made,

hemoglobin A1c values rise. This continues until the next dose of erythropoietin is given and the pattern repeats itself.

In these patients, hemoglobin A1c values cannot be accurately converted into mean blood glucose concentrations with any kind of confidence.

Bob Barrett: So, how did you perform the study?

Dr. Anders Berg: This work was performed in collaboration with Christiane Drechsler and Christoph Wanner from the University of Wuerzburg. They provided us with frozen longitudinal samples collected from 1,053 participants from the German Diabetes and Dialysis Study. All patients had diabetes mellitus and were already on hemodialysis at the time of enrollment. We used values for hemoglobin A1c and glycated albumin measured at enrollment, and after 6 and 12 months. Subject survival was then followed for an average of four years and we analyzed the association between glycated albumin values and patient survival.

Bob Barrett: And what were the key findings of your study and the implications of those findings?

Dr. Anders Berg: This is the largest study of its kind to date, associating glycated albumin measurements with survival risk in patients on hemodialysis. The strongest finding of our study is the clear association between very high glycated albumin values and increased future risk in patients on hemodialysis. There are two very important implications of this observation. The first obvious conclusions is that these results represent significant evidence corroborating past studies showing that glycated albumin measurements are predictive of future survival risk.

This finding, combined with previous studies showing the strong correlation between the glycated albumin and average blood glucose, together, suggest that glycated albumin may be a good therapeutic target for monitoring glycemic control and reducing adverse outcomes in patients on hemodialysis.

The second implication is that the increased survival risk in patients with high glycated albumin supports the original hypothesis that maintaining glycemic control may be important for improving outcomes in this patient population. Because of the inconsistent association in past studies between hemoglobin A1c and survival in dialysis patients, some kidney experts have indeed questioned whether glycemic control is important in these patients. Our results show that despite the many risk factors that patients on hemodialysis live with, chronically elevated blood glucose is

still associated with a significant amount of additional risk in these patients.

With this new test available, future studies may reveal that improving glycemic control by targeting glycated albumin may indeed improve outcomes in these patients.

Bob Barrett: And finally Dr. Berg, were there any limitations to your study?

Dr. Anders Berg: Although our analysis did not show a consistent association between elevated hemoglobin A1c values and survival risk, it is important to note that the statistical methods we used do not constitute a true head-to-head comparison of the prognostic value of hemoglobin A1c compared to glycated albumin.

Furthermore, this retrospective association study does not really constitute the level of evidence that a prospective clinical trial provides. In order to know with a use of glycated albumin tests, as a monitor for glycemic control and a target for making changes to hemodialysis patient's insulin and glucose lowering medications would affect patient outcomes, future perspective trials are needed. In other words, we still need to test whether modifying patient's medications based upon their glycated albumin measurements improves their clinical outcome.

Bob Barrett: Dr. Anders Berg is Assistant Director of Clinical Chemistry at Beth Israel Deaconess Medical Center in Boston, and an Assistant Professor of Pathology at the Harvard Medical School. He's been our guest in this podcast from *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.