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# Usefulness of Glycated Albumin Assay for Diabetes Monitoring

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## Abstract

In this issue of *Journal of Diabetes Science and Technology*, Kohzuma and colleagues describe a method for measuring glycated amino acids in albumin from serum samples. This method may be useful as an alternative to hemoglobin A1c in monitoring patients with diabetes in certain situations, e.g., diabetes patients with chronic renal failure. Because there are drawbacks of each analyte for measuring glycemic status, it is important to be able to clearly define what is being measured and determine what factors might interfere with each type of measurement. Once the utility of glycated albumin measurement is clearly defined and its use is accepted for diabetes care, standardization may be warranted.

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In an article entitled "Basic Performance of an Enzymatic Method for Glycated Albumin and Reference Range Determination" in this issue of *Journal of Diabetes Science and Technology*, Kohzuma and colleagues[1] evaluate the performance of the Lucica GA-L (Asahi Kasei Pharma, Tokyo, Japan), an enzymatic method for measurement of glycated albumin (GA) in serum. The authors show that the basic performance of the assay is good and that there is good sample and reagent stability. They also show that this assay is specific for the glycated amino acids in albumin and that the number of binding sugars to one GA is between one and three. This method correlates linearly with GA by high-performance liquid chromatography and also correlates well with isotope dilution mass spectrometry (IDMS), although no data were shown for the IDMS relationship. The reference range in an American population was 11.9–15.8%, which is close to the reference range determined in other populations.[2,3] Interestingly, there were significant differences between whites and blacks, with GA of whites being lower. This is in line with another study[4] showing ethnic differences in both GA and hemoglobin A1c (HbA1c) and supports the hypothesis of differences in glycemic status (i.e., mean blood glucose) between ethnic groups rather than differences in the relationship between glycation indices and mean glucose.

Their report is very timely in view of the fact that diabetes is rapidly increasing along with microvascular complications such as renal failure. Although HbA1c is the most useful measure of glycemic control in the vast majority of patients with diabetes, there are some situations that might require an alternative way to measure glycemic control. Hemoglobin A1c should not be used in any situation that causes a change in the average lifespan of the erythrocyte, such as in sickle cell anemia or sickle cell hemoglobin C disease, or in cases where the rate of hemoglobin glycation is altered,

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**Abbreviations:** (GA) glycated albumin, (HbA1c) hemoglobin A1c, (IDMS) isotope dilution mass spectrometry

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such as with some rare hemoglobin variants, including hemoglobins Raleigh, Gorwihl, and Rambam.[5–7] Even more importantly, there have been several reports suggesting the HbA1c provides inaccurate results in hemodialysis patients. In both Japanese and American diabetic subjects with renal disease, compared with those without, GA concentrations were significantly higher while HbA1c tended to be lower.[8,9] In addition, HbA1c has been positively associated with hemoglobin and negatively associated with the erythropoietin dose in hemodialysis patients, while these factors and serum albumin did not significantly impact GA levels.[9] In another study of patients on both hemodialysis and peritoneal dialysis, HbA1c significantly underestimated glycemic control relative to GA in both patient treatment groups.[10] Another study of patients with advanced chronic kidney disease (stage 3 or stage 4) but not on dialysis showed that HbA1c is also falsely reduced compared with GA.[11] This underestimation of glycemic control by HbA1c may be due to renal anemia, erythropoietin use, and/or dialysis; further studies are needed to be able to identify those patients who would benefit from glycemic control measurements other than HbA1c, such as GA. It is important to determine whether clinicians and patients are basing diabetes therapy on falsely low HbA1c results that could put patients at risk for more rapid progression of nephropathy to end-stage renal disease.

Unfortunately, there may also be interferences with the GA assay. While HbA1c measurement is affected by reduced erythrocyte survival or an increase in young erythrocytes (e.g., during treatment with erythropoietin-stimulating agents), GA can be influenced by factors that affect albumin turnover.[12–14] Because the majority of patients with advanced nephropathy have overt proteinuria, GA values may also be affected in these patients. One study has shown this to be the case; there was a significant decrease in GA values independent of glycemic state in diabetic patients with nephritic syndrome, while nonnephrotic range proteinuria did not significantly influence GA.[15]

Kohzuma and colleagues[1] discuss the differences in results reported from different GA methods, including thiobarbituric acid colorimetry, immunoassay, and enzymatic methods. Not only are the method principles different, but each may measure different numbers of glycation sites. This is somewhat analogous to measurements of total glycated hemoglobin by boronate affinity chromatography compared with HbA1c by either immunoassay or charge-based methods (e.g., ion-exchange high-performance liquid chromatography and electrophoresis). Harmonization studies with HbA1c and total glycated hemoglobin have clearly shown that different sites on hemoglobin appear to glycate proportionally, allowing for standardization or harmonization to a common reference value. The same is likely the case for GA where, as the authors show, their enzymatic method measures each glycation site (glycated amino acids in albumin) as does the thiobarbituric acid method, while chromatographic methods target the GA molecule and measure a glycated peak area that is compared with the total area of the albumin peak. Although GA is not currently standardized, the authors also mention an IDMS reference method for GA. It is certainly possible that different GA methods could be standardized to this reference if use of GA is increased and there is a need for standardization.

Neither HbA1c nor GA provide optimal estimates of glycemic control in all patients with diabetes. Further studies must be done to clearly define which marker is best for specific sub-groups of patients.

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