HHS Public Access

Author manuscript

Clin Chem. Author manuscript; available in PMC 2018 February 01.

Published in final edited form as:

Clin Chem. 2017 February ; 63(2): 447–449. doi:10.1373/clinchem.2016.265744.

Monitoring glycemic control in end stage renal disease: What should be measured?

Elizabeth Selvin[1] and **David B. Sacks**[2]

[1] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.

[2] Department of Laboratory Medicine, National Institutes of Health, Bethesda, MD.

Keywords

diabetes; hemoglobin A1c; glycated albumin; dialysis; chronic kidney disease; end stage renal disease

The study by Chen et al (1) in this issue of the journal addresses an important and practical problem, namely how to monitor glycemia in patients with end stage renal disease (ESRD). Recent estimates suggest that there are approximately 420 million people in the world with diabetes mellitus, a greater than 2.5-fold increase since the turn of the 21st century. The dramatic rise in the prevalence of diabetes is mainly due to the rise in type 2 diabetes resulting from the global increase in the burden of overweight and obese individuals. The complications of diabetes have risen concomitantly with the increasing numbers of persons with the disease. Diabetes is the leading cause of chronic kidney disease (CKD), and is one of the most important risk factors for ESRD, cardiovascular disease, infection and death in CKD patients (2). In the developed world, diabetes accounts for approximately 50% of ESRD cases, with the vast majority of these patients using dialysis as the primary mode of renal function.

Several analytes, including glucose, hemoglobin A1c (HbA1c), fructosamine, glycated albumin and 1,5 anhydroglucitol, are available for the evaluation of glycemia (3). Although widely available, blood glucose is limited by lack of sample stability, concentrations are altered by numerous factors (including diet, stress and illness), and it reflects glucose homeostasis at only a single point in time (4). HbA1c is the analyte most widely used to monitor long-term glycemic control. Glucose attaches to hemoglobin molecules over the lifetime of the red blood cell, which is approximately 120 days. Therefore, HbA1c reflects average glucose over the prior 8-12 weeks (5). HbA1c, which is used clinically to adjust therapy and as a marker of risk for the development of complications, is integral to the management of patients with diabetes and is also recommended for diagnosis. Nevertheless, HbA1c is sometimes altered in a glucose-independent manner, either by interference in the analysis or by conditions that change HbA1c unrelated to change in glucose. Assay interferences may include hemoglobin variants or certain drugs. In CKD, high blood urea concentrations result in increased protein carbamylation where isocyanic acid is attached covalently to arginine or lysine residues. Carbamylation of hemoglobin was a problem in HbA1c analysis in the past, but does not interfere in most modern methods (6). Nevertheless, HbA1c is potentially problematic as a measure of glycemic control in CKD due to

alterations in erythrocyte lifespan. Further, a common complication of CKD is anemia, which itself affects erythrocyte turnover and is commonly treated with iron and/or erythropoietin. These therapies can stimulate red cell production, increasing the number of young erythrocytes. In this setting, the proportion of hemoglobin molecules with glucose attached is lowered due to the shortened time for glycation, resulting in lower HbA1c than expected (2). Therefore, alternative markers of glycemia have been proposed for monitoring glycemic control in CKD patients. For example, in Japan, guidelines for monitoring glycemic control in diabetes patients on dialysis recommend glycated albumin over HbA1c.

Glucose attaches to many proteins in the body to form ketoamines. Plasma protein ketoamines are termed fructosamine, which includes all glycated plasma proteins. The most abundant protein in the blood is albumin, and nonenzymatic attachment of glucose to lysine residues on albumin produces glycated albumin. This post-translational modification reflects average glucose concentrations over the previous 14-21 days (equivalent to the half-life of albumin). Although approved in the USA by the Food and Drug Administration in the 1980s, early fructosamine assays were plagued by lack of specificity. Modifications to enhance specificity and other improvements have subsequently made the fructosamine assay a potentially useful alterative in situations where HbA1c is problematic.

Assays that measure glycated albumin are also commercially available. Although not as well studied as HbA1c, evidence is accumulating that glycated albumin measurement may have clinical value. For example, glycated albumin has been shown to perform well for the detection of patients with diabetes and may be useful to assess intermediate (2-4 week) glycemic control (3, 7). There is a growing body of data linking both glycated albumin and fructosamine to long-term complications (7-9), suggesting prognostic value that is similar to that of HbA1c in community-based populations. Since fructosamine and glycated albumin values are independent of erythrocytes, they are conceptually appealing as markers of glycemic control in those situations where erythrocyte lifespan is altered. Therefore, they have been advocated as better indicators than HbA1c of glycemia in individuals with ESRD (10, 11). However, the performance of fructosamine and glycated albumin as prognostic markers in patient populations with CKD, ESRD, or other conditions remains unclear. This is the gap in knowledge addressed by Chen et al (1).

The investigators conducted a prospective cohort analysis to examine the association of glycated albumin with mortality in a study population of 1,053 patients with diabetes mellitus who were receiving hemodialysis. They compare mortality risk associations for glycated albumin to those for HbA1c. Glycated albumin was measured in stored samples collected from participants at baseline, 6 and 12 months in the German 4D study, a randomized placebo-controlled trial of atorvastatin therapy. Median follow-up of participants was 4 years. HbA1c was measured as part of the original trial and testing was performed between 1998 and 2002. The investigators measured glycated albumin at a later time point (not specified in the paper) using an LC-MS/MS assay. The primary outcome of the 4D Trial was cardiovascular events, but the investigators chose to focus here on total mortality as the primary outcome (results for cardiovascular disease are not provided).

Chen et al (1) demonstrate that study participants in the highest quartile of baseline glycated albumin had a risk of total mortality higher than those in the lowest quartile. In general, findings for glycated albumin and HbA1c were similar, except results for glycated albumin, but not HbA1c, were statistically significant. The investigators also confirmed a lower correlation of glycated albumin with HbA1c in patients with ESRD as compared to normal subjects, a finding that has been shown in prior reports (12). Nonetheless, it is unclear to what extent the lower correlation in ESRD reflects non-glycemic alterations in HbA1c versus problems with glycated albumin in the setting of ESRD.

Notwithstanding these observations, there are some caveats that need to be borne in mind. Analogous to virtually all analytes used in patient care, glycated albumin is subject to some limitations. Several conditions alter glycated albumin independently of glucose. These include, among others, changes in albumin concentrations (e.g., nephrotic syndrome, protein losing enteropathy, malnutrition), cirrhosis, thyroid disease, hyperuricemia and smoking (13). Low albumin is of particular concern in the setting of ESRD. Chen et al measured glycated albumin by mass spectrometry, a method that is unlikely to be widely implemented. Although they compared their assay to an enzymatic method (Lucica GA-L Asahi Kasei Pharma Corp) widely used in Japan, there was a proportional bias of 20% at low glycated albumin values. This difference emphasizes an important problem with glycated albumin analysis, namely the absence of standardization. Comparison of methods reveals up to a 20-fold difference in reference intervals (14), considerably impairing clinical utility. Moreover, caution should be exercised in interpreting the HbA1c findings of the report as the method used to measure HbA1c was not NGSP-certified. This is unfortunate as these results cannot be compared to other clinical studies. It is surprising that an NGSP-certified method was not used; NGSP certification commenced in 1996, before 1998 when sample collection began in the study. Another difficulty in interpretation of the findings is the absence of any clear dose-response association of either glycated albumin or HbA1c with mortality risk. In the crude analysis (shown in the Kaplan-Meier analysis in Figure 2 in Chen et al) and other models, sometimes patients with higher categories of baseline glycated albumin or HbA1c actually have better survival than those in the lower groups. The time-varying results are also unexpected in that associations for HbA1c are not at all consistent with the baseline analysis. One worries that the results of the study are highly model dependent and potential non-linear relationships of glycated albumin and HbA1c with mortality have not been adequately accounted for in the analyses. Furthermore, ESRD is a complicated condition and patients are at high risk for mortality. Hyperglycemia may simply be a less potent risk factor in this population, particularly for all-cause mortality.

How should chronic glycemia be evaluated in diabetic patients with ESRD? A report of a joint consensus conference on diabetic kidney disease convened by the American Diabetes Association, the American Society of Nephrology and the National Kidney Foundation was published in 2014 (2). The authors recommended that “specific decisions on therapy should be based on self-monitoring of blood glucose”. Measurement of HbA1c was also advocated “as the trending of the levels can assist in therapy decisions”. Should glycated albumin and/or fructosamine now replace HbA1c to monitor glycemia in diabetic patients with ESRD? Although fructosamine and glycated albumin are being increasingly evaluated in clinical studies (11, 15), the overwhelming body of evidence on glycemic control in ESRD

to date has been obtained using HbA1c. As described above, all measures of glycemia are subject to limitations in the setting of ESRD. What is required is a large prospective study that evaluates the different glycemic analytes with continuous glucose monitoring as the gold standard to provide a better assessment of the patient's true glycemic status.

Acknowledgments

Research Funding: D.B. Sacks, Intramural Research Program of the National Institutes of Health (NIH). E. Selvin was supported by NIH/NIDDK grants K24DK106414, 2R01DK089174 and R01DK108784.

Nonstandard abbreviations

CKD	chronic kidney disease
ESRD	end stage renal disease
HbA1c	hemoglobin A1c

References

1. Chen, et al. Clin Chem. 2016 TEMPORARY REFERENCE.
2. Tuttle KR, Bakris GL, Bilous RW, Chiang JL, de Boer IH, Goldstein-Fuchs J, et al. Diabetic kidney disease: A report from an ada consensus conference. Diabetes Care. 2014; 37:2864–83. [PubMed: 25249672]
3. Parrinello CM, Selvin E. Beyond hba1c and glucose: The role of nontraditional glycemic markers in diabetes diagnosis, prognosis, and management. Curr Diab Rep. 2014; 14:548. [PubMed: 25249070]
4. Sacks DB. A1c versus glucose testing: A comparison. Diabetes Care. 2011; 34:518–23. [PubMed: 21270207]
5. Goldstein DE, Little RR, Lorenz RA, Malone JI, Nathan D, Peterson CM, Sacks DB. Tests of glycemia in diabetes. Diabetes Care. 2004; 27:1761–73. [PubMed: 15220264]
6. Little RR, Rohlfing CL, Tennill AL, Hanson SE, Connolly S, Higgins T, et al. Measurement of HbA(1c) in patients with chronic renal failure. Clin Chim Acta. 2013; 418:73–6. [PubMed: 23318566]
7. Selvin E, Rawlings AM, Grams M, Klein R, Sharrett AR, Steffes M, Coresh J. Fructosamine and glycated albumin for risk stratification and prediction of incident diabetes and microvascular complications: A prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) Study. Lancet Diabetes Endocrinol. 2014; 2:279–88. [PubMed: 24703046]
8. Nathan DM, McGee P, Steffes MW, Lachin JM, DCC/EDIC Research Group. Relationship of glycated albumin to blood glucose and HbA1c values and to retinopathy, nephropathy, and cardiovascular outcomes in the DCCT/EDIC study. Diabetes. 2014; 63:282–90. [PubMed: 23990364]
9. Selvin E, Rawlings AM, Lutsey P, Maruthur N, Pankow JS, Steffes M, Coresh J. Fructosamine and glycated albumin and the risk of cardiovascular outcomes and death. Circulation. 2015
10. Vos FE, Schollum JB, Walker RJ. Glycated albumin is the preferred marker for assessing glycaemic control in advanced chronic kidney disease. NDT Plus. 2011; 4:368–75. [PubMed: 25984197]
11. Freedman BI, Andries L, Shihabi ZK, Rocco MV, Byers JR, Cardona CY, et al. Glycated albumin and risk of death and hospitalizations in diabetic dialysis patients. Clin J Am Soc Nephrol. 2011; 6:1635–43. [PubMed: 21597024]
12. Peacock TP, Shihabi ZK, Bleyer AJ, Dolbare EL, Byers JR, Knovich MA, et al. Comparison of glycated albumin and hemoglobin A(1c) levels in diabetic subjects on hemodialysis. Kidney Int. 2008; 73:1062–8. [PubMed: 18288102]

13. Welsh KJ, Kirkman MS, Sacks DB. Role of glycated proteins in the diagnosis and management of diabetes: Research gaps and future directions. Diabetes Care. 2016; 39:1299–306. [PubMed: 27457632]

14. Kohzuma T, Yamamoto T, Uematsu Y, Shihabi ZK, Freedman BI. Basic performance of an enzymatic method for glycated albumin and reference range determination. J Diabetes Sci Technol. 2011; 5:1455–62. [PubMed: 22226265]

15. Shafi T, Sozio SM, Plantinga LC, Jaar BG, Kim ET, Parekh RS, et al. Serum fructosamine and glycated albumin and risk of mortality and clinical outcomes in hemodialysis patients. Diabetes Care. 2013; 36:1522–33. [PubMed: 23250799]