Assessment of Glycemic Control in Dialysis Patients with Diabetes: Glycosylated Hemoglobin or Glycated Albumin?

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The natural history of diabetes is characterized by the variable occurrence and severity of microvascular (nephropathy, retinopathy, neuropathy) and macrovascular (atherosclerotic cardiovascular) complications. A large body of laboratory data lends credence to the argument that hyperglycemia is central to the genesis and progression of both micro- and macrovascular complications of diabetes. This notion, however, has been only partially validated. Several large randomized, controlled trials have consistently demonstrated that aggressive glycemic control slows the appearance and/or progression of microvascular complications (1–3). However, the evidence that aggressive glycemic control ameliorates the macrovascular complications in individuals with diabetes is less robust (2–4).

ESRD is an extreme manifestation of diabetic nephropathy, a microvascular complication of the disease. Individuals with diabetic ESRD remain at risk for the appearance and progression of other microvascular complications, including retinopathy and neuropathy. It is instructive to remember that diabetes is the most common cause of blindness and nontraumatic amputation in many industrialized nations, and the subgroup with ESRD is at substantially higher risk for these dreaded complications. However, the burden of macrovascular disease in these patients is considerably higher. The annual mortality of dialysis patients with diabetes in the United States exceeds 22%, and up to one-third of these deaths are classified as "sudden cardiac deaths" (5). The importance of aggressive glycemic control in dialysis patients with diabetes has never been directly tested. Extrapolating the data from other populations with diabetes, it may be reasonable to expect that aggressive glycemic control would reduce the progression of microvascular complications of diabetes in the subgroup undergoing dialysis. However, whether improvements in glycemic control will substantially affect macrovascular complications is less clear. Not only is there insufficient evidence of benefit in populations with diabetes without ESRD, but also the vascular disease associated with uremia is even more complex. Indeed, even interventions such as lipid lowering with statins, which have consistently been demonstrated to reduce death risk in other populations, have not been successful in reducing the mortality in the broad spectrum of dialysis patients with hyperlipidemia (6,7). Notwithstanding these caveats, routine monitoring of and ensuring adequate glycemic control is an important component of the overall management of dialysis patients with diabetes.

In clinical practice, glycemic control is best assessed by a combination of home blood glucose monitoring and quarterly measurement of glycosylated hemoglobin (HbA_{1c}). The degree of glycosylation of hemoglobin depends not only on the level of glycemic control but also on the half-life of red blood cells. Because ESRD is characterized by reduced red blood cell survival, concern has been raised about the adequacy of HbA_{1c} as a measure of glycemic control in dialysis patients (8). The pioneering work by Freedman and colleagues (9,10) in the past 4 years, including the article published in this issue of *CJASN* (11), has questioned whether glycated albumin should replace HbA_{1c} to monitor glycemic control in these patients. Glycated albumin is a ketoamine formed by the binding of glucose to albumin by nonenzymatic oxidation (12). The percentage of albumin that is glycated is a measure of shorter term glycemic control than is HbA_{1c} (2 to 3 weeks *versus* 1 to 2 months) (12). In choosing between these tests, two important questions need to be answered. First, what is the relationship between glycemic control and each of these measures among dialysis patients with diabetes? Second, is there evidence to support the argument that using glycated albumin in lieu of HbA_{1c} is better in preventing microvascular and macrovascular complications in this high-risk population with diabetes?

At least three studies have examined the interrelationships among blood glucose, $HbA_{1c,}$ and glycated albumin in dialysis patients with diabetes (8–10). In each of these studies, for any given level of blood glucose, the HbA_{1c} value was demonstrably lower in dialysis patients than in control subjects with diabetes and without nephropathy. In contrast, there was no difference between the relationship of blood glucose levels and percentage of glycated albumin in dialysis patients with diabetes or control patients without nephropathy. Put differently, the ratio of HbA_{1c} to gly-

cated albumin was 30% to 40% higher in dialysis patients than in control subjects with diabetes and without nephropathy (8–10). These findings raise concern that HbA_{1c} underestimates the degree of hyperglycemia in dialysis patients, suggesting that if a clinician were to use the same thresholds for HbA_{1c} as in the general population, then diabetes would be undertreated. However, these studies cannot be considered definitive. In each of these studies, anywhere from one to three nonfasting glucose measurements from the preceding few months were used as the gold standard (8–10). Although the selection of such infrequent nonfasting measurements in relatively large cohort studies is understandable, this should also give us pause before we seek to abandon the time-tested HbA_{1c} as a measure of glycemic control. Furthermore, albumin homeostasis is often abnormal in patients with ESRD, and it is important to consider potential inaccuracies in glycated albumin in addition to the limitations of HbA_{1c} as a potential explanation for the higher HbA_{1c}–glycated albumin ratio in ESRD. Indeed, it may be easier to implement different thresholds for HbA_{1c} in ESRD and non-ESRD populations than undertake the studies necessary to replace HbA_{1c} with glycated albumin.

The second question is perhaps clinically more relevant: Will the use of glycated albumin in lieu of HbA_{1c} allow physicians to achieve better glycemic control and, hence, offer a superior measure to use to reduce micro- and macrovascular complications of diabetes? In this issue of *CJASN*, Freedman *et al.* (11) measured quarterly glycated albumin and HbA_{1c} in 444 prevalent dialysis patients with diabetes (401 hemodialysis, 43 peritoneal dialysis). During 2.33 years of follow-up, 156 patients died. Using a time-dependent proportional hazards model, each 5% increase in glycated albumin was associated with 14% higher risk for all-cause mortality in the best-fit model (11). In contrast, there was no association between HbA_{1c} or blood glucose on death risk (11). These findings stand in contrast to two large studies—one each in hemodialysis (n = 23,618) and peritoneal dialysis (n = 2798) patients—demonstrating a robust and linear increase in all-cause mortality with increasing HbA_{1c} levels (13,14). Furthermore, a *post hoc* analysis of the 1255 hemodialysis patients who had diabetes and were enrolled in Die Deutsche Diabetes Dialysis Studie (4D) also showed a graded increase in sudden cardiac death with higher HbA_{1c} levels (15). What could be the potential reasons for the discrepancy between the article by Freedman *et al.* and these previous studies? First, the risk with glycemic control is cumulative and is best captured in a time-dependent or time-averaged analysis; the greater the number of measurements of the risk factor of interest, the better captured is the cumulative risk. In the analysis by Freedman *et al.* (11), the median number of HbA_{1c} measurements was far fewer than for glycated albumin (three *versus* eight). It is important to note that in the study by Williams *et al.* (16), the only large study unable to demonstrate an association between HbA_{1c} and mortality, only a single baseline measurement of HbA_{1c} was used for analysis. Second, the number of events in the article by Freedman *et al.* (11) is relatively small, limiting the statistical power to demonstrate associations.

Notwithstanding these differences, does the study by Freedman *et al.* (11) provide incontrovertible evidence for the superiority of glycated albumin over HbA_{1c}? Perhaps not just yet. As discussed, even though the investigators were unable to demonstrate an association between HbA_{1c} and mortality in dialysis patients, other studies have (13–15,17). Furthermore, the hypothesis that using glycated albumin in lieu of HbA_{1c} provides better prevention of macrovascular complications of diabetes still remains untested. Finally, the greatest demonstrable benefit of aggressive glycemic control is in retarding progression of microvascular and not macrovascular complications; there are no published data on glycated albumin *vis-à-vis* microvascular complications in patients with diabetes and with or without ESRD.

To summarize, Freedman *et al.* (11) have almost singlehandedly advanced our understanding of the limitations of assessing glycemic control using HbA_{1c} in dialysis patients with diabetes and have underscored the potential role of glycated albumin for this purpose. However, the current body of evidence is still insufficient to conclude that use of glycated albumin better predicts glycemic control and consequent morbidity or mortality in patients with ESRD and diabetes when compared with HbA_{1c}. Furthermore, given the differences in half-lives of red blood cells and albumin, adequate monitoring of glycemic control would require a monthly measurement of glycated albumin compared with a quarterly measurement of HbA_{1c}. This, in turn, would add to the overall expense. Given the limitations of the existing data, it seems premature at this early stage to abandon HbA_{1c} in favor of glycated albumin. Given that almost half of the patients in the United States with ESRD experience diabetic complications and their death rate from vascular events exceeds that of individuals without diabetes, prospective studies directly designed to determine the best measures of glycemic control, coupled with studies to determine the best target values to reduce diabetic complications, would go a long way to improve care in this vulnerable population.

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Disclosures

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See related article, "Glycated Albumin and Risk of Death and Hospitalizations in Diabetic Dialysis Patients," on pages 1635–1643.