Editorial

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Glycemic Control Assessment in the Dialysis Patient: Is Glycated Albumin the Answer?

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In this issue, Divani et al. [1] have shown that glycated albumin (GA) correlates better than hemoglobin A1c (A1c) with one week's worth of blood glucose levels obtained by continuous glucose monitoring (CGM) in diabetic patients on hemodialysis. It should be pointed out that *both* were highly correlated with the CGM-obtained average glucose values (GA $r = 0.884$; A1c $r = 0.694$). This has been shown previously in a number of studies with less intense glucose monitoring but whether GA should replace A1c in the assessment of glycemic control in dialysis patients is controversial [2–5]. Since GA reflects glucose levels only for about 2 weeks, it would be expected to correlate better with CGM done for that prior week than A1c, which reflects glucose levels for the prior 3–4 months. In end stage renal disease (ESRD), there is decreased red blood cell (RBC) survival with younger RBCs and A1cs generally measure about 1% lower than expected for given levels of glucose [2]. With iron and erythropoietin treatment, the gap for A1c widens and when patients have nephrotic range proteinuria GA measurements become less accurate [5]. With both GA and A1c, there are direct relationships between increasing levels of GA or HbA1c and mortality [6–9] and some studies show a higher correlation with mortality with GA compared to A1c [6, 8]. In addition, with A1c some studies show a "U"-shaped curve, with low and high levels both being associated with increased mortality [10–12].

What does all of this mean to the clinician caring for the patient? The benefits of achieving A1c levels ~7% in decreasing the development and progression of earlier stages of chronic kidney disease (CKD) were shown unequivocally by the DCCT/EDIC study, ADVANCE and other studies [13, 14]. Once a patient reaches ESRD, however, there are only cross-sectional studies showing the GA-associated increased mortality and the U-shaped curve for A1c, which show the nadir for mortality being in the measured 7–8% range [10, 11]. If the ~1% "correction" factor is applied, then perhaps the nadir for risk for mortality may be closer to 8–9% as measured in a non-ESRD patient.

The increase in mortality at the lower side of this U-shaped curve is due to the increased hypoglycemia known to occur with ESRD patients [15]. The lower the glomerular filtration rate, the greater the risk of hypoglycemia, with the greatest risk being in stage 5 CKD [15]. Although some oral agents can be safely used in patients on dialysis, most diabetic patients with ESRD, in fact, are treated with insulin [16] and this use of insulin creates an increased risk for hypoglycemia. The kidney is responsible for 30–80% of insulin removal [17]; reduced kidney function results in a prolonged insulin half-life and a decrease in in-

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sulin requirements [17]. Furthermore, the usual gluconeogenic capacity of the kidney is reduced in these diseased kidneys, hampering the ability to recover from hypoglycemia [18]. Severe hypoglycemia is markedly increased in patients with ESRD who are treated with insulin [19]. As most clinicians can attest, the life of the dialysis patient can be difficult and erratic. Too often I have heard statements like "…my ride to the dialysis unit was late, so I took my insulin but didn't have time to eat". Given this increased risk of hypoglycemia and its attendant morbidity, the U-shaped curve for mortality with a nadir "measured" A1c around 7–8% suggests that such levels would seem to be a reasonable goal for most patients.

But what about GA? The curves relating A1c to average glucose and GA to average glucose are not parallel. Most patients have had A1c levels measured during their pre-ESRD lives and when the ~1% correction factor should be applied is not clear. When GA becomes a more accurate reflector of average glucose is also not clear and how to convert the A1c to GA values is uncertain in a given patient. Although Tahara has shown in diabetic patients without CKD that a 1% increase in A1c corresponds to a 4% increase in GA [20], no such study has been done in patients on dialysis, and because of the anemia and protein issues, this relationship may well not hold. How well standardized GA measurements are from one laboratory to another is not known. If a patient goes to different dialysis units that use different laboratories, are the GA values going to be comparable? How often should GA be measured? It reflects only 2 weeks' worth of blood glucose levels and an acute illness could cause a substantial rise in GA that does not then warrant longer-term changes in treatment. At least with A1c, there is an international standardization of the measurement and it does not have to be done more frequently than every 3 months. However, neither GA nor HbA1c may be good indicators of an individual patient's level of glycemic control, given the widespread values for either when plotted against the average glucose levels [1, 2, 21]. Finally, the measurements that are most important to the patient on a day-by-day basis are the capillary blood glucose levels, which are used to determine adjustments and changes in insulin dosing. CGM is an advance in technique over the standard capillary glucose measurements, but, as this study showed [1], they are very highly correlated.

In dialysis patients as in others, we want to achieve glucose levels as close to normal as possible without hypoglycemia in order to prevent/delay the progression of other long-term complications such as retinopathy, neuropathy and cardiovascular disease. But the risk/benefit ratio has changed and therefore, the glycemic goals have changed too. Patients receiving dialysis are fragile with respect to glucose homeostasis and are at high risk for hypoglycemia. The GA and A1c levels that are ideal to delay onset and early progression of CKD and other complications are too low for the dialysis patient and it is the daily capillary blood glucose levels that are needed to guide changes in insulin dosing. Given all the problems outlined above for GA, it is not clear to me that the time has come to replace A1c with GA. For dialysis patients taking insulin, neither can substitute for capillary blood glucose measurements, which should be done at least 4 times per day to avoid hypoglycemia and decrease hyperglycemia.

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