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Albuminuria is Your Guide to Assessing Future GFR Slope

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The traditional view of diabetic kidney disease (DKD) involves the development of albuminuria, followed by a steady decline in the glomerular filtration rate (GFR). End-stage kidney disease and ranges in GFR decline from >40% to 57% (doubling of serum creatinine) are often used in clinical trials as validated clinical end points to demonstrate differences between novel and established therapies. The caveat, however, is that substantial time is needed to confirm these differences. Therefore, developing outcome trials to evaluate new agents for kidney disease progression is very challenging and expensive. It is worth noting that the median follow-up of appropriately powered clinical trials focused on primary renal outcomes was 35 months.[1]

The slope of GFR decline has been used in clinical trials as an alternative indicator of kidney disease progression, with the common assumption that the GFR decline follows a linear path downward. This is a convenient assumption that is easy to apply to practice. Unfortunately, the linearity assumption is an oversimplification of the process. It has been challenged recently by others and in the current report by Yamanouchi *et al.*[2] in this issue of the journal. Their study included 319 patients from the longitudinal cohort of the Toranomon Natural History Study of Diabetic Kidney Disease. This cohort spans over 30 years, with biopsy-proven DKD.[2] Through sophisticated and robust statistical means, Yamanouchi *et al.*[2] demonstrated that GFR fluctuations were predominantly curvilinear, with high variability in albuminuria.

The patient population studied was unlike most Western people, which were relatively lean. The median GFR was 31.6 ml/min per 1.73 m^2, with a median albumin-to-creatinine ratio of 2205 mg/g. Biopsy-proven class 3 and 4 DKD was present in 54.8% of patients. After a median follow-up of 3.3 years, 11% of patients regressed to lower albuminuria levels, an effect likely attributed to receiving appropriate therapy. However, it is noteworthy that only about 70% of the Yamanouchi *et al.*[2] cohort patients received a renin-angiotensin (RAS) blocker, and dosing was unclear. This is important because low to moderate doses of these agents have not been proven to slow DKD progression or reduce mortality.[3] Albuminuria was stable in 56% of patients throughout the study. The median compound annual increase for albuminuria was 43.6%, with 84.5% of patients developing nephrotic-range proteinuria by the study end. One should remember that the guideline goal for albuminuria reduction associated with a slowed decline in kidney function is a minimum sustained reduction of >30% below the baseline level.[4]

One of the study's essential and notable findings was establishing an association between estimated GFR decline and albuminuria levels, as depicted in Figure 2 of the Yamanouchi and colleagues.[2] Progression to end-stage kidney disease was rather exponential as albuminuria increased, vastly affecting the GFR slope and shape. The inflection point of the exponential change in albuminuria was between 1 and 2 g, where the GFR slope sharply steepened. This highlights the importance of both of the following: (i) following albuminuria clinically over time and more frequently as GFR declines to levels well below 45 ml/min per 1.73 m^2 and (ii) reducing albuminuria below 1 g per day, with the premise of slowing chronic kidney disease (CKD) progression as has been shown in all renal outcome trials dating back to the 1990s. Other factors affecting the GFR slope but less predictable include age, smoking, and uncontrolled hypertension, among others.[5] In the current study, all patients who developed end-stage renal disease had albuminuria. Thus, the findings are restricted to this albeit large group of patients with DKD.

The observations by Yamanouchi and colleagues are restricted to people with high levels of

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albuminuria, and the authors postulate that studies of patients who do not have albuminuria and progress to end-stage kidney disease may have a different diagnosis than diabetic nephropathy.[6] This assertion by the authors points to a weakness in generalizing these data because it is well known that people with diabetic nephropathy progress to end-stage kidney disease even without albuminuria; therefore, this may be perceived as a limitation of their findings because those patients were selected for a biopsy due to some concern of potentially having a different diagnosis than DKD.

In addition, only 14% of patients with albuminuria in the range of 300 to 3000 were receiving optimally dosed RAS blocker therapy by the end of the study. Therefore, guideline-directed therapy was not employed to achieve maximum benefit. Moreover, only 22.7% of patients with albuminuria >3000 mg/g were receiving optimized RAS blockade. This underdosing of RAS blockade most certainly influenced the rate of CKD progression and GFR slope as a whole. It would be interesting to do a similar evaluation using the established pillars of the therapy approach to maximally slow diabetic nephropathy progression and see the slope relationships in that setting.[7] Notwithstanding, the slopes as a whole would be significantly softened with appropriate RAS blockade first and with the addition of goal-directed therapies that include sodium-glucose transport protein 2 inhibitors and the nonsteroidal mineralocorticoid antagonist, finerenone, which have been proven to improve renal outcomes in randomized controlled trials.[7]

The results from Yamanouchi and colleagues are validated by other publications that studied GFR slopes in patients with CKD of various etiologies. A recent analysis of the FIDELITY outcome database ($N = 12,512$) encompassing 2 large statistically powered outcome trials in people with DKD.[8] This analysis showed very clearly that in the presence of maximally tolerated doses of RAS blockade coupled with the nonsteroidal mineralocorticoid receptor blocker, finerenone, and median urinary albumin-to-creatinine ratio of 514 mg/g, a reduction ≥30% was observed in 3338 (53.2%) patients in the finerenone group compared to 1684 (27.0%) patients in the placebo group receiving RAS inhibition alone. Reduction in urinary albumin-to-creatinine ratio (analyzed as a continuous variable) mediated 83% of the treatment effects of the kidney outcomes. The authors of this analysis concluded that in patients with DKD from type 2 diabetes, early albuminuria reduction accounted for a large proportion of the treatment effects against CKD progression and a modest proportion of the impact against cardiovascular outcomes.

Using Bayesian methodology, Li *et al*.[9] showed that a substantial number of patients from the African American Study of Kidney Disease cohort (all had advanced hypertensive CKD) had nonlinear GFR trajectories or had prolonged periods of nonprogression after a mean follow-up of 12 years.[9] Jiang and colleagues also demonstrated significant heterogeneity in long-term GFR decline in a cohort of 10,129 Chinese patients with type 2 diabetes. Patients classified as rapid decliners using the linearity assumption had marked heterogeneity in GFR decline over a median follow-up of 11.8 years.[5] Similar to the study by Yamanouchi and colleagues, albuminuria and, in this case, diabetic retinopathy were found to be the strongest predictors of GFR decline. Those cohorts have been followed for more than 10 years, giving ample time for the GFR slope to declare itself and for trends to be apparent.

What the current study does best is highlight the close and robust correlation between albuminuria and GFR. The rapid decline in kidney function is associated with an increased risk of mortality, and predicting the rate of progression is fundamental in improving long-term outcomes in patients with CKD. Early rapid GFR loss is a significant predictor of future GFR loss when normoalbuminemic patients with type I diabetes advance through CKD stages, adding to the value and utility of the GFR slope in assessing clinical outcomes. The slope decline even preceded albuminuria onset in this setting.[S1]

When combined with albuminuria, GFR slope decline becomes a powerful tool in studying CKD progression as a surrogate end point for kidney failure, and this is gaining traction when considering future clinical trials in patients with CKD.[S2] Over the past few years, what has happened has been groundbreaking in kidney outcome trials, with new therapies that are significantly improving renal and cardiovascular outcomes. The current study, among others, paves the way for conducting more trials with clinically-relevant renal end points that will enhance the care of patients with CKD as a whole, with a better understanding of their clinical course based on integrating this information into practice.

In short, the trajectory of the GFR slope decline is not linear but somewhat curvilinear. It is affected by many dynamic factors, with relative periods of stability that may be more prevalent than previously appreciated. This better understanding will help design future studies that closely investigate the association of time-varying risk factors, such as blood pressure and

albuminuria, with changes in kidney function.

DISCLOSURE

GLB serves as a consultant and on executive committees of clinical trials associated the following companies: Novo Nordisk, Bayer, Astra Zeneca, INRegen, Alnylam, Idorsia. OAD declare no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (WORD)

Supplementary References.

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