Improvemen in Kidney Function: A Real Occurrence

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CKD is thought traditionally to follow an unremittingly progressive decline over time. Because of this, guidelines and public health campaigns have focused on early detection and treatments directed to slow the progression of CKD and delay the onset of ESRD. Progression of kidney disease has been studied in both observational and clinical trial settings.1–7 However, there has been considerable variability in progression reported, ranging from rapid progression to nonprogressive stable kidney function to an improvement in kidney function over time.2,6–8 Recent studies that attempted to characterize patients who experience an improvement in kidney function were plagued by the variability inherent in serum creatinine measurements used to estimate GFR.

In this issue of JASN, Hu et al.9 report improvement in kidney function among a subset of patients with hypertensive CKD. The authors use data from the AASK (The African-American Study of Kidney Disease and Hypertension) trial,3,10 which was designed to evaluate the effect of BP and antihypertensive drug therapy on the rate of decline of renal function in participants with mild-to-moderate chronic renal insufficiency caused by hypertension. The participants were 1094 African Americans 18–70 years of age, with GFRs between 20 and 65 ml/min per 1.73 m² at enrollment. Kidney function was determined by direct measurement of GFR from 125I-iothalamate clearances for the trial phase of the study. An equation was derived from this measured GFR data to estimate GFR (eGFR) using serum creatinine. This eGFR was used for the longitudinal assessment of kidney function.

To avoid the acute hemodynamic changes in eGFR related to drug interventions, the authors focused on chronic eGFR slopes among the 949 participants with three or more eGFR measurements (61% male) with a baseline mean age of 55 (SD:11) years. During the 8.8 years of follow-up, the median number of eGFR measurements was 16. Bayesian linear mixed effects models were applied to derive the probability that each patient’s true underlying slope was greater than zero and could not be explained by random measurement variation; clear improvers were defined as patients with a probability of at least 0.95 of having positive eGFR slopes. Among the participants, 3.3% (n=31) demonstrated clear positive eGFR slopes—that is, an improvement in kidney function over time. The mean slope of these patients was +1.06 (SD: 0.12) ml/min per 1.73 m² per year, compared with −2.45 (SD: 0.07) ml/min per 1.73 m² per year among remaining patients. Relative to nonimprovers, improvers were more likely to be younger, have low baseline proteinuria, and lower BP goal assignment at randomization. Younger age and lower levels of proteinuria were associated with improvement in kidney function in the multivariate model.

Methodological and analytical differences across studies make it difficult to directly compare results from prior studies to those reported by Hu et al. However, several prior studies have also reported improvements in kidney function in a subset of patients over time. As many as 19% patients with a GFR between 25 and 55 ml/min per 1.73 m² in the Modification of Diet in Renal Disease study had stabilization or improvement of their renal function during the 2-year follow-up. Eriksen and Ingebretsen,2 examining 3047 Norwegian clinical practice patients with stage 3 CKD, reported that 27% did not experience a decline in GFR during the mean observation period of 4 years. In a recent study, Al-Aly et al.,8 studying the Veteran Affairs cohort of 4171 patients with early CKD (eGFR between 59 and 45 ml/min per 1.73 m²), reported that after a median observation period of 2.6 years, 38% patients with stage 3 CKD maintained stable kidney function. Similarly, Perkins et al.,6 studying 15,465 patients receiving primary care through a large integrated health care system, reported that approximately one-third of patients had an increase in eGFR over the follow-up period.

In the study by Hu et al.,9 baseline proteinuria was lower among improvers than nonimprovers, and in multivariate analysis, the authors demonstrate that reduction in proteinuria was associated with improvement in eGFR. These results add to prior studies demonstrating the importance of proteinuria as a prognostic marker and specifically that the prognosis associated with a given level of kidney function varies significantly based on the presence and severity of proteinuria.11–14 Although the paper of Hu et al.9 is interesting because it demonstrates that true improvement in eGFR (confirmed by direct measurement of kidney function) can occur over
time, it also raises some important questions. In particular, the prognostic implications of an improvement in kidney function over time are not addressed in this study. An improvement in kidney function in general is expected to be associated with a more favorable health status; however, recent studies5-8 report that improvement in eGFR over time is associated with adverse outcomes. Perkins et al.6 demonstrated that both declining and increasing eGFR over time associate with an increased risk of death compared with stable kidney function. Similarly, Al-Aly et al.8 reported that, compared with the patients with mild CKD progression, patients with nondeclining kidney function (rate of eGFR change >0 ml/min per 1.73 m² per year) exhibited a trend toward increased risk of death. Similarly, Matsushita et al.,5 studying the Atherosclerosis Risk in Communities cohort, also reported that increasing eGFR is associated with increased risk of adverse outcomes.

The study by Hu et al.9 was rigorously conducted and sheds light on this important issue of the dynamics of change in renal function. The completeness of the baseline clinical data, by the virtue of the initial well designed clinical trial, enabled an accurate assessment of factors associated with improvement in kidney function. Robust statistical analysis methods also allowed the authors to account for the common biases encountered in slope analysis. There are, however, a few limitations, appropriately acknowledged by the authors, which should be kept in mind while interpreting the study results. The study population was very selective; thus, the generalizability of the results is limited. Although the authors used robust statistical methods, the phenomenon of regression to the mean cannot be excluded. Finally, the study sample was small and points toward the necessity to explore this issue in a larger cohort. Despite these limitations, the study by Hu et al. highlights the potential that eGFR may improve over time among a subset of patients. Further studies in this area are required to characterize the improvers, as well as to determine the prognostic implications of an improvement in eGFR.

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DISCLOSURES

None.

REFERENCES