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See related article, "Loss of Klotho Contributes to Kidney Injury by De-repression of Wnt/ $\beta$ -Catenin Signaling," on pages 771–785.

## Physical Performance and All-Cause Mortality in CKD

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It is well documented that measures of exercise capacity and physical performance are impaired in people with ESRD who are undergoing maintenance dialysis therapy.<sup>1–3</sup> Several studies have also described impaired exercise capacity in CKD patients who have lesser degrees of reduced GFR, and who are not receiving chronic dialysis treatment.<sup>4,5</sup> The causes for impaired exercise capacity and physical performance are not entirely clear. A number of adverse conditions have been associated epidemiologically with these impairments, including physical deconditioning, muscle atrophy, anemia, a propensity toward increased serum inflammatory markers, and lower quality of life.<sup>4,6,7</sup> The relative contributions of these putative causes to impaired exercise capacity and reduced physical performance are not well defined.

Another poorly explored area is the clinical consequences to CKD patients who manifest these disorders. No one, to my knowledge, has previously reported whether reduced exercise capacity or physical performance associates with increased morbidity or mortality in nondialyzed CKD patients. The article published by Roshanravan *et al.* in this issue of *JASN* is unique in that it is the first to address the question of whether physical performance is associated with mortality rates.<sup>8</sup> It examined this question in 385 patients who were not receiving chronic dialysis therapy, but had stage 2–4 CKD. Patients were recruited from two prospective cohorts: the Seattle Kidney Study and the University of Maryland Study of Chronic Kidney Disease. There were some differences in the characteristics of the patients in these two separate cohorts, but these differences would not be expected to invalidate the results of the study.<sup>8</sup> Physical performance was measured by usual gait speed (walking 4 m at the patient's usual pace), timed up and go test (TUAG) (time to stand from a seated position and walk around a cone placed 4 m distant), 6-minute walking distance, and handgrip strength (HGS). For some study participants, the reduction in GFR was rather modest. The inclusion criteria required the estimated GFR (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration study equation<sup>9</sup> to be  $<90$  ml/min per 1.73 m<sup>2</sup>. Other inclusion criteria were that the patient was not receiving chronic renal replacement treatment at the time of the physical performance assessment, did not have a stroke, was not using a wheel chair, and had completed at least one physical performance measurement. Mortality rate was monitored over a median duration of 3 years.

The mean age of the participants was  $61 \pm 13$  years, and the mean eGFR was  $41 \pm 19$  ml/min per 1.73 m<sup>2</sup>. The results of this innovative study indicate that measures of physical performance of the lower extremities were at least 30% below predicted values and were strongly associated with mortality rates. Each 0.1-m/s decrement in gait speed was associated with a 26% higher risk for all-cause death (hazard ratio, 1.26; 95% confidence interval, 1.09 to 1.47). Each 1-second longer TUAG was associated with an 8% higher risk for all-cause death (hazard ratio, 1.08; 95% confidence interval, 1.01 to 1.14). In contrast, HGS was relatively well preserved and not

strongly associated with mortality. On the basis of receiver operating curve analyses, gait speed and TUAG measurements were stronger predictors of mortality during the median 3-year follow-up period than were the eGFR or a number of commonly used biomarkers of morbidity in CKD patients including serum albumin, C-reactive protein, phosphate, bicarbonate, and blood hemoglobin.

This article confirms the important finding that people with mild to moderate renal insufficiency have a substantial reduction in measured physical performance, especially in the lower extremities.<sup>5,8</sup> In addition, these reductions in physical performance, specifically in usual gait speed and TUAG, are rather strongly associated with all-cause mortality.

Roshanravan *et al.* appropriately indicate several limitations in their study. First, the authors point out that this study does not demonstrate that the low physical performance is a cause of the mortality risk in their patients. In addition, the relatively low number of deaths, presumably due to the rather short median follow-up period, may reduce the precision of true associations between physical performance measures and mortality. This might account for the rather surprisingly small reduction in HGS. It might also account for the lack of significant association between HGS and mortality in the CKD patients, which stands in contrast to previously reported findings in elderly non-CKD populations.<sup>10</sup> Moreover, the data collected in this study concerning physical performance and daily physical activity were not of sufficient size to carefully assess for causal relationships between physical performance and reduced physical activity in this CKD population.

It is also important to underscore another important qualification of this study. It is not clear to what extent the impaired physical performances or their association with the mortality rate is due to CKD or to sequelae from CKD. It is possible that, despite adjustments for age, sex, race, and some comorbid risk factors, the reduced physical performance and its association with mortality may be due to other morbid factors that are not caused by CKD. Indeed, these other morbid factors might themselves be causes of CKD or promote the loss of GFR in people who have established CKD. An argument in favor of this possibility is that substantial numbers of people in this study had only modest reductions in eGFR: stage 2 or stage 3A (eGFR from 59 to 45 ml/min per 1.73 m<sup>2</sup>) CKD. Whether these higher levels of GFR in CKD patients, independent of comorbid conditions, are associated with inflammation, oxidative stress, carbonyl stress, protein-energy malnutrition, or other metabolic abnormalities that might impair physical performance is not clear. It is well documented that physical performance in elderly individuals without CKD is significantly associated with mortality,<sup>10–12</sup> and many of the same causal factors may be operative in stage 2–4 CKD.

Notwithstanding these concerns, the study by Roshanravan *et al.* constitutes an important contribution. It demonstrates

for the first time that people with mild to moderate CKD (stages 2–4) who demonstrate impaired physical performance concerning the lower extremities (usual gait speed and TUAG) are at increased risk for mortality. Further studies will be necessary to examine the causal factors that are responsible for these findings. Given the current high interest in the problem of frailty in CKD patients,<sup>3,5,7</sup> it can be anticipated that much new information on this question will become available in the near future.

## DISCLOSURES

The author is a consultant to Pinta Biotherapeutics, Inc.

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See related article, “Association between Physical Performance and All-Cause Mortality in CKD,” on pages 822–830.