

Urinary Creatinine and Survival in CKD

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Low muscle mass is associated with risk of CKD progression, cardiovascular disease events, and mortality in a variety of settings (1). It is widely hypothesized that these associations may be confounded by conditions associated with low muscle mass, including frailty, poor physical fitness, poor nutritional status, and greater comorbidity. However, low muscle is also hypothesized to worsen insulin resistance and inflammatory stress, and therefore, it is also possible that low muscle mass may be causally related to adverse clinical outcomes.

Although many would consider the clinical gold standard for quantification of muscle mass to be whole-body magnetic resonance imaging, this measure is rarely done (2). However, other methods, such as dual-energy x-ray absorptiometry (DXA) (3), bioelectric impedance, and urine creatinine appearance rate (4), have been validated as reasonable surrogates. Although these measures are all strongly correlated with muscle mass and one another, they may provide insights to different aspects of muscle health above and beyond their relationship with the mass of muscle *per se*. For example, in the general population, low DXA fat-free mass measurements have not consistently been associated with mortality (5), whereas lower urine creatinine appearance rate has consistently been associated with the same outcome (6–8).

Much less is known about the effect of muscle mass and quality in CKD, particularly in non-ESRD settings. In this issue of *CJASN*, Wilson *et al.* (9) evaluate the relationship between fat-free mass (as measured by both bioelectric impedance and DXA) and 24-hour urine creatinine appearance rate with risk of mortality and ESRD in the large Chronic Renal Insufficiency Cohort (CRIC) in patients with CKD stages 3 and 4 at baseline. For the first time, this study compares the relative strengths of association of the different markers of muscle mass with clinical outcomes in a large representative population with CKD (9). Similar to findings in the general population, the investigators report that low urine creatinine appearance rate is much more strongly associated with both mortality and ESRD than bioelectric impedance.

The findings reported by the investigators raise an important new question. Why would lower urine creatinine appearance rate be so much more strongly associated with risk of mortality and ESRD than other—arguably more precise—measures of muscle mass, such as DXA and bioelectric impedance? As suggested above, one intriguing possibility is that the urine creatinine appearance rate may provide

information regarding muscle quality or improved metabolism above and beyond muscle mass. Perhaps muscle quality is the stronger indicator of wellbeing than mass of muscle *per se*. Perhaps a more robust diet higher in protein intake or a lifestyle with greater resistive exercise promotes muscle quality and also leads to both a higher urine creatinine appearance rate and a better prognosis at any given amount of muscle mass. Perhaps there are new unidentified factors influencing creatinine generation from muscle in patients with CKD.

We must also consider that the disparate strengths of association with outcomes reported here and elsewhere may reflect bias in one or more of the muscle measurements. This is particularly relevant to urine creatinine appearance rate, because its measurement depends on accurate timed urine collections, which are known to be fraught with inaccuracies in the outpatient setting. In any study that depends on the participant to independently collect their urine, usually for 24 hours, with strict instruction but without supervision, there is considerable opportunity for erroneous over- or undercollection. It could reasonably be expected that the sickest, oldest, and least medically literate participants might be those most likely to undercollect their urines. If so, this systematic undercollection may make it such that low urine creatinine appearance rate would mark these important adverse health indicators above and beyond low muscle mass or low muscle quality. Wilson *et al.* (9) should be commended for their thorough efforts to investigate this possibility through multiple sensitivity analyses within their study. For example, they exclude subjects when urinary creatinine appearance rate fell outside of 30% of predicted values on the basis of validated equations (10). This analysis resulted in exclusion of 37% of the cohort who may have under- or overcollected their urines (9). Within the subset of retained individuals, the correlation of urinary creatinine appearance rate with muscle mass measured by DXA and bioelectric impedance was much higher than that observed in the whole cohort (9). These data suggest that the sensitivity analysis was effective in excluding at least those individuals with the most severe under- and overcollections, and therefore, findings of relationships of urine creatinine appearance rate with outcomes within the subset retained in the sensitivity analysis may be particularly reliable, despite the smaller available sample size. Importantly, even within this subset, the associations of urine creatinine appearance rate with ESRD

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and mortality were quite strong and essentially unchanged from those observed in the whole cohort.

Although spot urine specimens have largely replaced timed urine collections to assess severity of albuminuria, timed collections remain an integral part of contemporary nephrology practice for a variety of other clinical indications, including assessment of dietary intake of micronutrients (e.g., sodium, phosphate, and protein) and evaluation of the etiology of nephrolithiasis. They are unlikely to disappear from clinical practice in the near future. The timed urine collection also has some unique advantages, including that it is relatively inexpensive and widely available worldwide. In light of the findings by Wilson *et al.* (9), it is important for clinicians and researchers alike to recognize that low urine creatinine appearance rate is a robust risk marker for adverse outcome. This finding is quite strong and thus far, consistent across studies. In the CRIC, Wilson *et al.* (9) had the unique opportunity to assess multiple measurements of muscle mass concurrently in the same individuals, allowing them to advance the intriguing novel hypothesis that urine creatinine appearance rate may reflect more than simply muscle mass. What we need now are studies that determine factors above and beyond collection inaccuracies and muscle mass that might influence urine creatinine appearance rate. Such factors may provide new opportunities for interventions to improve muscle mass, muscle function, diet, or other as-yet-unidentified factors linked with low urine creatinine appearance rate. If such factors are modifiable, they may hold promise for new treatments that may ultimately translate to improved quality and length of life in patients with CKD.

Disclosures

None.

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