A Good Reason to Measure 24-Hour Urine Creatinine Excretion, but Not to Assess Kidney Function

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Collection of a 24-hour urine sample and measurement of creatinine clearance made up the standard of care for assessing kidney function for years until regression formulas for estimation of GFR were developed. As a result, 24-hour urine sample collection is used much less frequently in current practice. However, this test may have other utilities in addition to assessing kidney function. In this issue of CJASN, Di Micco et al. (1) followed the changes in daily urine creatinine excretion over a median of 6 years in a relatively large group of patients with stage 3–5 CKD. The authors demonstrated a mean annual decline of 16 mg in 24-hour urinary creatinine excretion among patients with stage 3 and 4 CKD. There were a 3% higher all-cause mortality and 2% higher rate of initiation of dialysis for each 20-mg/d annual decrease in creatinine excretion after adjustment for patient demographic characteristics, comorbid conditions, and inflammation. This important and provocative study informs us and should lead to more questions that demand answers.

Total daily excretion of creatinine has been widely accepted as a tool to assess muscle mass in humans and animals. This is based on the fact that almost all of the body’s creatine is found in skeletal muscle and that it is converted nonenzymatically and at a constant rate to creatinine. The only route of elimination for creatinine in individuals with normal kidney function is renal excretion, which is expected to be constant and equal to its production at steady state (2). Therefore, total daily excretion of creatinine at steady state would be proportional to total-body creatine content and total-body skeletal muscle mass. Daily urinary creatinine excretion has shown good correlation \( r=0.7 \) with fat-free body mass as assessed by skin-fold thickness and bioelectrical impedance (3) and an almost-perfect correlation \( r=0.99 \) with lean body mass, as assessed by whole \(^{82}\)K count in human studies (4).

Daily excretion of creatinine varies by 4%–8% irrespective of diet and physical activity. Strenuous exercise and a diet high in animal protein may increase daily excretion of creatinine (2,4). Not only the type of diet but the way it is prepared can influence creatinine excretion. Numerous drugs also affect creatinine concentration and its excretion or interfere with its assays. In addition, creatine supplements can be associated with an increase in serum creatinine as well as an increase in creatinine excretion.

Among individuals with diabetes, variation in daily creatinine excretion is much higher: 15% in women and 17.4% in men (5). Despite these shortcomings, for many investigators daily urinary excretion of creatinine remains the method of choice for assessing total muscle mass because other available methods are more costly and less reproducible. These include dual-energy x-ray absorptiometry, computed tomography, and magnetic resonance imaging.

Investigating the relationship between muscle mass and mortality is of great importance. Current clinical practice is focused mainly on the relationship between obesity (and body mass index [BMI] as a measure of its severity) and both cardiovascular (CV) and all-cause mortality. However, Romero-Corral and colleagues’ meta-analysis of 40 studies (including >25,000 participants) (6) showed that although a BMI <20 kg/m\(^2\) was associated with a 37% higher risk of all-cause mortality and a 45% higher risk of CV mortality compared with a BMI of 20–25, individuals with BMI of 30–35 did not have higher all-cause or CV mortality. Even severely obese participants (BMI >35) were not at increased risk of all-cause mortality compared with those with a BMI of 20–25 (6).

The association between lower muscle mass, as evidenced by lower daily creatinine excretion and higher all-cause and CV mortality, was shown in a prospective study of more than 8000 participants from the general population in The Netherlands (7). In that study, baseline daily urinary excretion of creatinine showed an inverse association with mortality, which was stronger in men than women, and with major cardiovascular events, which was stronger in women than in men (7).

The Heart and Soul Study investigated this relationship in 903 individuals with established coronary artery disease and showed a 2.3-fold higher death rate among the participants in the lowest tertile of daily creatinine excretion compared with participants in the highest tertile after adjustments for age, sex, BMI, estimated GFR, and CV risk factors (8). Similarly, among 604 renal transplant recipients followed for an average of 5.3 years, those in the highest tertile of daily urinary creatinine excretion had a 60% lower risk of death and 60% lower risk of graft loss compared with those in the lowest tertile (9).

The intriguing concept that creatinine excretion can predict outcomes also lends itself to future studies. For
instance, long-term supplementation of patients with crea-
tine, along with muscle-building exercise programs, might be followed longitudinally to ascertain whether outcomes were improved and were reflected in the urine creatinine. Likewise, agents that have anabolic capabilities, such as growth hormones and ghrelin mimetic growth hormone secretagogues, could likewise be followed for muscle mass and creatinine excretion.

The strength of Di Micco and colleagues’ study over previously published studies in this field is its longitudinal de-
sign. In addition to demonstrating an inverse correlation between the baseline daily creatinine excretion and mortal-
ity, the authors showed a positive correlation between the magnitude of decrease in daily creatinine excretion (loss of muscle mass) over the period of follow-up and mortality in patients with CKD. Another attractive feature is that it is the first study that looks at changes in daily creatinine excretion as a marker of change in muscle mass in patients with CKD. The relatively large sample size and the relatively long follow-up period are among other strengths of this study.

The study has some shortcomings. First, the study shows that a decline as small as 20 mg/d in daily creatinine ex-
cretion is associated with higher mortality. However, a small change like this (≤2%) is well within the variability of the test used to measure creatinine. Although this finding may apply to a population as a whole, its application to the daily practice may not be feasible. Second, because no individ-
uals with normal GFR were included in the study as a control group, it is not clear how the rate of decline in daily excretion of creatinine in different stages of CKD would compare with that in individuals with normal GFR. Addi-
tionally, it is important to know whether the association between changes in creatinine excretion and mortality would be stronger in CKD than the general population. Third, although degradation of creatinine in normal indi-
viduals is negligible, it may increase to as high as 66% in CKD. Yet, as mentioned by the authors, it is important to know whether the association between changes in creatinine excretion and mortality might be expected because age and sex are considered major determinants of total body muscle mass and it is also known that chronic illness can be associated with loss of muscle mass.

Creatinine has been much maligned in nephrologists’ quest for the perfect GFR determination and has been largely ignored in the enthusiastic search for multiple glitzy biomarkers of innumerable diseases affecting the kidney (13). We speak with disdain about the lowly serum creat-
inine and the total inadequacy of either serum creatinine or creatinine clearance/excretion unless appropriately beau-
tified by exotic GFR modeling. Indeed, for the purposes of an increasingly accurate and valid estimated GFR, this may be true (14). However, Di Micco and colleagues’ interesting paper raises the possibility that we should look at the urine creatinine in a rejuvenated fashion—that, like the phoenix, perhaps the lowly creatinine can tell us much more than a poor GFR or a state-of-the-art biomarker for kidney function or muscle mass. Future studies will be needed to tease out the role of urine creatinine as a biomarker of “things to come.” Perhaps it can pave the way to early intervention in CKD to circumvent the dreaded downstream effects of poor nutrition, decreased muscle mass, and reduced quality of life that have been front and center of outcomes for our patients with progressive kidney disease. At the very least, this obser-
vation should encourage us to obtain urinary creatinine and interpret them in the context of something more than a less-than-adequate estimated GFR.

Disclosures
None.

References
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