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Relationship Between Renal Function and Functional Decline: Role of the Estimating Equation

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Abstract

Background—Several formulas are available to estimate glomerular filtration rate (GFR) at the bedside. A decrease in GFR has been associated with poorer performance. We hypothesized that it is related to worsening disability as well. The aim of this study was to evaluate whether the Modification of Diet in Renal Disease formulas can predict worsening disability better than the classic Cockcroft-Gault formula or the measured creatinine clearance.

Methods—We studied 666 participants in the InCHIANTI study with 6 years of follow-up data. We evaluated whether directly measured creatinine clearance and GFR estimated using the Modification of Diet in Renal Disease and Cockcroft-Gault formulas predict new disability defined as the loss of 1 ADL over the 6-year follow-up.

Results—The mean age was 73.1 years (SD: 6.1), 57.7% were women. Fewer than 5% of participants were disabled at baseline. Eighty-one (12.2%) participants experienced a decline in activities of daily life score at follow-up. Declining GFR was associated with increasing risk of worsening disability (Mantel-Haenszel $P < .001$), with an increased steepness in the curve at GFR below 60 mL/min. The relative risks for worsening disability in people with GFR less than 60 mL/min/m were 3.19 (95% CI: 2.12–4.79) and 4.40 (95% CI: 2.80–6.94) using the Modification of Diet in Renal Disease and the Cockcroft-Gault equations, respectively. The corresponding figures obtained with measured creatinine clearance was 3.95 (95% CI: 2.60–6.01). After adjustment for potential confounders, however, these estimates were substantially reduced.

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Conclusion—Estimation of renal function with the Cockcroft-Gault or Modification of Diet in Renal Disease formulas can help to identify elderly at risk of worsening disability. The mechanism by which reduced kidney function predicts disability should be further investigated.

Keywords

Renal function; disability; aged; estimating equations

Estimation of renal function is of paramount importance in clinical practice, but direct assessment of glomerular filtration rate (GFR) requires complex and time-consuming techniques such as Iothalamate or Iohexol clearance, and it is rarely performed in the clinical setting. For this reason, several formulas, for example the Cockcroft-Gault (CG)¹ or the Modification of Diet in Renal Disease (MDRD),² have been developed to estimate GFR at the bedside. Renal function estimated using these predicting equations is associated with clinical outcomes such as mortality and cardiovascular events in the elderly.³ A decrease in GFR has also been associated with decline in physical performance, possibly because of heightened inflammatory state.⁴ Given this association between GFR and performance, we hypothesized that renal function may also be associated with worsening disability in the elderly population. The aim of this study **was** to evaluate whether reduced renal function is associated with incident disability, and whether GFR estimated **using** the MDRD formulas can predict worsening disability better than the classic Cockcroft-Gault formula or the measured creatinine clearance.

Methods

Data Source

We used data from the InCHIANTI study, which was designed to investigate the factors contributing to the decline of mobility in older persons.⁵ Participants in the study were randomly selected from the populations of 2 town areas in the Chianti region: Greve in Chianti and Bagno a Ripoli. The Italian National Institute of Research and Care on Aging ethical committee ratified the study protocol. Participants received an extensive description of the study and signed an informed participation consent that included permission to conduct analyses on the biological specimens collected and stored. For those unable to fully consent because of cognitive or physical problems, surrogate consent was also obtained from a close relative. The eligible participants were interviewed at their homes by a trained study researcher using a structured questionnaire aimed at investigating their health status, their physical and cognitive performance, and other factors possibly related to loss of independence in late life. The interview was followed by a physical examination at the study clinic during which a blood sample was drawn. Serum creatinine was measured using a modified Jeffé method, as reported elsewhere.⁶ Creatinine clearance was measured using the 24-hour urine collection method. Follow-up assessments were performed at 3 and 6 years.

Sample Selection

We excluded participants with age younger than 65 years and those without baseline serum creatinine measurement. We included for the longitudinal analyses only those patients who had an evaluation of the physical performance at the 6-year follow-up visit (n = 666).

Analytic Approach

We described the population using descriptive statistics (mean and standard deviation for continuous variables; proportion for categorical variables). To provide information on the prognostic value of the GFR estimated using different formulas we evaluated their ability to predict loss of at least 1 activity of daily living (ADL: eating, bathing, washing, dressing, getting in and out of bed, moving around the house, toilet use) between baseline and 6-year follow-up. We calculated the relationship between GFR (10 mL/min/1.73 m reductions) and worsening disability using Mantel-Haenszel for linear trend. We also calculated the relative risk of worsening disability associated with GFR less than 60 mL/min/1.73 m compared with those with GFR $\geq$ 60 mL/min/1.73 m. Estimates of these effects were also calculated after adjusting for baseline age, gender, and conditions that are associated with declining renal function and physical performance, including heart failure, diabetes mellitus, chronic obstructive pulmonary disease, obesity (body mass index [BMI] $\geq$ 30), cognitive decline (Mini-Mental State Examination <24), and number of ADLs that participants were already unable to perform at baseline. We directly compared the predictive capacity of the different methods using the areas under their receiver operating characteristic curves (AUC). Analyses were performed using SAS V9.0 for Windows (SAS Institute, Cary, NC) and Stata V10 (Stata Inc., College Station, TX).

Results

The general characteristics of the 666 participants are shown in Table 1. The mean age of our sample was 73.1 years (SD: 6.1, range: 65–98), and 57.7% were women. Fewer than 5% of participants were disabled at baseline.

GFR estimated by the MDRD (76 mL/min/1.73 m) and directly measured as creatinine clearance (79 mL/min) were substantially similar. The CG formula yielded a somewhat lower average value (67.6 mL/min).

Of the 666 participants included in the study, 81 (12.2%) experienced a worsening in ADL disability at follow-up. The ADL that was most frequently lost was bathing (13.1%), followed by dressing (11.1%) and toilet use (8.4%). The ADL least frequently lost was eating (3.6%). In Figure 1 we show the relationship between worsening disability and GFR estimated by the measured creatinine clearance, MDRD, and CG equations. All the measures of GFR were positively associated with increased risk of disability progression (Mantel-Haenszel $P < .001$ for all), and such relationship was steeper for GFR values below 60 mL/min.

The relative risks for worsening disability associated with GFR lower than 60 mL/min/m were 3.19 (95% confidence interval [CI]: 2.12–4.79) and 4.40 (95% CI: 2.80–6.94) for the MDRD and the CG equations, respectively. The corresponding relative risk for creatinine clearance was 3.95 (95% CI: 2.60–6.01). After adjustment for potential confounders, however, these estimates were substantially reduced (Table 2).

The AUC obtained using the CG formula was 0.754, compared with 0.643 obtained with the MDRD formula (Figure 2, $P < .001$). The best cutoff for the CG was 59.4 mL/min

(sensitivity: 73%, specificity: 69%). At the 60 mL/min cutoff level, sensitivity was 71% and specificity was 69%.

Discussion

Our data show that renal function estimated with either the MDRD or the CG formulas is independently associated with an increased risk of worsening disability.

To our knowledge, this is the first study quantifying the risk for disability associated with renal function estimated with different formulas. In the National Health and Nutrition Examination Survey population, a reduction in GFR, estimated using the CG formula, was associated with lower baseline values of different indices of physical activity (activity variety, activity frequency, metabolic equivalents).⁷ In a cross-sectional survey of a representative sample of the Australian population, a GFR lower than 60 mL/min estimated by the CG formula was associated with a lower score in the Physical Function Subscale of the Short Form 36 questionnaire.⁸ In the Nurses Health Study, reduced kidney function estimated by the MDRD formula was associated with a decrease in the Physical Function Subscale score.⁹ Similar results were found in the Heart and Estrogen/Progestin Replacement Study.¹⁰ In a cohort of elderly community-dwelling people who were free of disability at baseline, renal function estimated with either MDRD or cystatin C was associated with decline in physical function, although only the association with the MDRD-estimated GFR was still statistically significant after adjustment for markers on inflammation.⁴ Finally, renal function estimated using the MDRD formula was associated with functional outcomes after hemorrhagic stroke,¹¹ but not after ischemic stroke.^{11,12}

The relationship between renal function and physical performance is complex and still not fully understood. Sarcopenia is common in renal insufficiency, and its prevalence increases as GFR declines.¹³ In rodents, this association is mediated by different mechanisms, including defects of the insulin/insulinlike growth factor 1 intracellular signaling processes that cause muscular protein degradation through the ubiquitin-proteasome pathway.^{14,15} In humans, insulin resistance is present already in the early stages of renal disease,^{16,17} is negatively correlated with GFR,¹⁸ and is involved in muscle wasting mediated by the ubiquitin-proteasome pathway.¹⁹ The same pathway can be activated by inflammatory mediators¹⁹ that are elevated in renal insufficiency.²⁰ In epidemiological studies, increase of interleukin (IL)-6 has been associated with functional decline.²¹ The negative effect of renal failure on physical performance may also be mediated by vitamin D deficiency. Vitamin D is increasingly recognized as a pleiotropic hormone acting also on muscle. Skeletal muscle has vitamin D receptors,²² and vitamin D deficiency can cause myopathy of varying severity;²³ furthermore, vitamin D deficiency has been associated with reduced physical performance.²⁴

The association we found between worsening disability and the MDRD and CG formulas may be explained by the fact that these formulas may “capture” different clinical characteristics beside GFR. For example, estimation provided by the CG formula is influenced by body weight and BMI,²⁵ which in turn are related to adverse outcomes in the elderly. Supporting this hypothesis, in the same InCHIANTI population GFR is associated with mortality only when estimated using the CG formula.⁶ The MDRD formula, in

contrast, has been shown to provide GFR estimates that are associated with cardiovascular events and mortality in both the general population and in randomized clinical trial samples.^{26,27} It should be kept in mind, however, that these formulas have been developed in young-adult populations (mean age <50 years) with renal insufficiency, and their performance in an elderly population with characteristics similar to ours has never been evaluated. Furthermore, the concordance of the different formulas is variable, especially in the elderly.^{28–30} As a consequence, it may also be the case that in this population the CG formula provides a better estimate of the GFR compared with the MDRD. This would explain the association between the CG formula and worsening disability even after adjustment for BMI, body composition, and age, which are known to increase the bias of this formula.²⁵ The association we found between our outcome and measured creatinine clearance seems to support this hypothesis. Nonetheless, it must be remembered that creatinine clearance measured with the 24-hour urine collection method has been criticized, as it may be even more biased than formula-based estimations.³¹

Some limitations of this study must be taken into account. GFR was not directly measured, and therefore our data cannot be used to improve our understanding about the best formula to use for GFR estimation in community-dwelling elderly people. Another issue is that we used the CG formula without adjustment for body surface area, and this may have biased our results. Our findings, however, confirm the prognostic role of this formula that have already been shown in other studies; furthermore, when the CG was normalized for body surface area the results were virtually unchanged (data not shown). Finally, despite its simplicity from an arithmetical point of view, the CG formula requires anthropometric data that may be not so easy to obtain in elderly people. Height, for example, may be underestimated because of osteoporosis; as a consequence, the generalizability of our results may be suboptimal.

In conclusion, we have shown that estimation of renal function with the CG and the MDRD formulas can help to identify elderly at risk of worsening disability. The available knowledge, however, does not allow discrimination between whether the increased risk is because of renal function itself, or because of other unmeasured factors influencing the estimation. More studies are needed to identify the most reliable equation to estimate GFR in the elderly, and then to verify whether renal function has a direct effect on the risk for disability.

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Fig. 1.
Relationship between GFR estimated according to 3 different methods and loss of at least 1 ADL.

Fig. 2. Areas under the ROC curves obtained using the CG or MDRD formulas ($P < .001$ for the comparison between the 2 AUCs).

Table 1

General Characteristics of the Population

N	666
Mean age, y	73.1 (SD: 6.09)
Women, %	57.7
Mean serum creatinine	0.90 (SD: 0.17)
Mean measured creatinine clearance	79.0 (SD: 24.5)
Mean estimated creatine clearance (CG)	67.6 (SD: 17.8)
Mean estimated GFR (MDRD)	76.6 (SD: 16.0)
Prevalence of disability, %	3.2

CG, Cockcroft-Gault; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

Table 2

Risk of Loss of at Least 1 ADL in Participants with GFR <60 mL/min

	Unadjusted RR (95% CI)	Adjusted* RR (95% CI)
MDRD	3.19 (2.12–4.79)	1.72 (1.09–2.70)
CG	4.41 (2.80–6.94)	1.90 (1.11–3.26)
Measured creatinine clearance	3.95 (2.60–6.01)	2.09 (1.28–3.41)

ADL, activity of daily living; CG, Cockcroft-Gault; CI, confidence interval; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; RR, relative risk.

* Adjusted for age; gender; diagnoses of diabetes mellitus, heart failure, chronic obstructive pulmonary disease; lean/fat cross-sectional area at 38% of tibial length.