Estimating renal function in older people: a comparison of three formulas

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Abstract

Background: estimation of the glomerular filtration rate (GFR) at the bedside is important because renal insufficiency is related to increased mortality and morbidity. A discrepancy between the Cockroft–Gault (CG) and the Modification of Diet in Renal Disease (MDRD) formulas has been observed in older people.

Objective: to compare the GFR of inpatients aged 65 or older estimated using the CG and two of the MDRD formulas.

Setting: acute care geriatrics and internal medicine wards.

Subjects and methods: data come from the Gruppo Italiano di Farmacovigilanza nell’Anziano (GIFA). To quantify the agreement between the formulas, we used the 95% limits of agreement, the κ statistic and a graphic approach to evaluate the influence of potential confounders on the magnitude of the difference in the GFR estimates.

Results: we studied 7,747 persons [51.1% women, mean age 77.8 (SD 7.2)]. The mean GFR estimated using the CG, MDRD1 and MDRD2 formulas was 51.2 ml/min (21.3), 54.9 ml/min (19.8) and 64.7 ml/min (24.2), respectively. At the individual level, the MDRD formulas can yield estimates that differ by more than 50% compared with the CG formula. The formulas showed a moderate agreement in diagnosing moderate renal insufficiency and a fair agreement in diagnosing severe renal insufficiency. The magnitude of the difference in GFR estimates was influenced by age and weight.

Conclusions: the CG and MDRD formulas have a good average agreement, but at the individual level, they can give estimates that differ substantially, and cannot be used interchangeably to measure renal function in elderly people.

Keywords: aged, aged 65 and over, renal failure, estimating formulas, elderly
Introduction

Estimation of glomerular filtration rate (GFR) at the bedside is important because renal insufficiency is related to increased mortality, risk of cardiovascular events and morbidity [1, 2]. Several formulas have been developed to estimate the GFR [3–5], because serum creatinine (SC) alone is frequently normal also in people with reduced GFR [6]. Older and malnourished patients are at special risk of having depressed GFR but normal SC [6, 7], and older patients in the acute care hospital are a population at special risk of having concealed renal failure, because the effects of an acute illness are added to those of chronic conditions. Recognising these patients is important because depressed GFR requires that the doses of drugs cleared by the kidney be proportionally reduced to prevent adverse drug reactions (ADRs) and nephrotoxic drugs be avoided. Adverse drug reactions account for up to 3.4% of all the admissions to the acute care hospital in populations over 65 and frequently complicate the hospital stay [8, 9], and it is likely that at least part of these ADRs could be avoided by correctly dosing drugs. Unfortunately, none of most commonly used equations achieved an optimal mix of accuracy and precision in a young-adult population [10]. Furthermore, a noticeable discrepancy between the Cockroft–Gault (CG) and the Modification of Diet in Renal Disease (MDRD) formulas, the most widely used, has been observed in a large population over 65 living in long-term facilities [11], and these formulas have been found to miss a consistent proportion of patients with renal failure within a population of octogenarian patients [12].

To better understand the differences in the GFR estimated with different formulas, we compared the results of the CG and MDRD formulas in older people admitted to acute care wards. The aim of the study was to quantify the discrepancy between the GFR estimated by the CG formula (CG-GFR) and the MDRD formulas (MDRD1-GFR and MDRD2-GFR) and to verify whether the magnitude of the discrepancy is influenced by potentially confounding factors.

Patients and methods

The present study uses data from the Gruppo Italiano di Farmacovigilanza nell’Anziano (GIFA) study, a large collaborative observational study group based in community and university hospitals located throughout Italy that since 1988 periodically surveys drug consumption, occurrence of ADRs and quality of hospital care [13]. We used data on patients consecutively admitted to the participating centres during the 4 month surveys conducted in 1993, 1995, 1997 and 1998. We excluded two study periods (1988 and 1991), because in those surveys not all laboratory data were collected. A study physician with specific training completed a questionnaire for each patient admitted to the participating wards without inclusion or exclusion criteria and updated it daily. Data recorded included socio-demographic characteristics, medical variables, laboratory, neuropsychological and physical function variables. Procedures conformed to guidelines provided by the Catholic University Ethical Committee.

Estimation of the GFR

For all subjects, GFR estimate was calculated by CG [3], MDRD1 [4] and MDRD2 [5] formulas as follows:

CG formula:

$$\text{CG-GFR} = \frac{(140-\text{age}) \times \text{weight in kg}}{(72 \times \text{SC})} \times 0.85 \text{ if woman}$$

MDRD1:

$$\text{MDRD1-GFR} = [170 \times (\text{SC})^{-0.999} \times (\text{age})^{-0.176} \times (\text{blood urea nitrogen})^{-0.170} \times (\text{serum albumin})^{0.318}], \times 0.762 \text{ if woman}$$

MDRD2:

$$\text{MDRD2-GFR} = [186.3 \times (\text{SC})^{-1.154} \times (\text{age})^{-0.203}], \times 0.742 \text{ if woman}$$

Height and weight were measured while the patient was fasting and wore light clothing. Weight of dehydrated or oedematous patients was measured after the achievement of the euvolemic status. Serum creatinine concentration was determined at discharge.

Analytic approach

We analysed the demographic characteristics of participants, and calculated the prevalence of selected disease (renal and cardiovascular, diabetes and chronic obstructive pulmonary disease), of physical impairment (defined as needing help in performing at least one of the activities of daily living) and of cognitive impairment (defined as scoring 7 or less on the Hodkinson abbreviated mental test) [14]. We quantified the agreement between the formulas using the 95% limits of agreement [15] that are calculated as the average difference ±1.96 × SD of the average difference. Because exploratory analyses showed an increasing variability of the average difference for higher values of the estimated GFR, we used a log transformation, obtaining 95% limits of agreement for the ratio MDRD-GFR : CG-GFR. We also compared the CG-GFR and MDRD-GFR using the weighted $\kappa$ statistic to quantify their degree of agreement in identifying people with normal or mildly reduced renal function [estimated GFR >60 ml/min/1.73 m² body surface area (BSA)], moderate renal failure (estimated GFR between 30 and 60 ml/min/1.73 m² BSA, inclusive) and severe renal failure (estimated GFR <30 ml/min/1.73 m² BSA) [16].

There are factors, such as gender or weight, that may affect differentially the precision of the estimation of the formulas, increasing the disagreement between them. To evaluate the role of some of these variables, we used a graphic approach plotting the difference of the values obtained by the two formulas on the value of the variable of interest and using local regression techniques [17] to fit a non-parametric curve smoothing the relationship between the two variables.

While the MDRD formulas are corrected for BSA, the CG formula is not. Discrepancies between the methods could be because of this difference and, therefore, we also
checked the agreement after correction of the CG estimate for the BSA, calculated as \([(\text{height} \times \text{weight})/3600]^{1/2}\) [18].

**Results**

Among 22,403 patients aged 65 and older in the GIFA study, 12,778 were enrolled in the selected periods. After exclusion of patients for whom it was impossible to calculate the GFR because of missing data, the final sample size was 7,747. Because information on weight was required and this measurement is more difficult to obtain in people with severe functional impairment, patients selected in the sample had a lower prevalence of physical disability and were accordingly slightly older and more frequently women. In turn, included patients had a minimally increased prevalence of ischaemic heart disease, diabetes mellitus and heart failure (HF) (see supplementary data Appendix 1 at http://www.ageing.oxfordjournals.org/). The mean age was 77.8 years (SD 7.2, range 65–104 years), 51.1% of them were women. The mean SC concentration was 1.19 mg/dl (SD 0.72). The prevalence of an established diagnosis of renal disease was 494 of 7,747 (6.4%), while 1,526 (19.7%) participants had diabetes and 1,185 (15.3%) HF.

The mean estimated GFR was 51.2 ml/min (SD 21.3) using the CG formula, 54.9 ml/min/1.73 m^2 BSA (SD 19.8) using the MDRD1 and 64.7 ml/min/1.73 m^2 BSA (SD 24.2) using the MDRD2 formula.

Figure 1 shows the difference between the log values of CG-GFR and MDRD1-GFR plotted against the average of the two estimates. The CG formula tends to underestimate the GFR, with a mean log-difference of –0.085, that is to say that the CG formula on average underestimates the GFR by 9% relative to the MDRD1 formula. While this can appear a small error, the 95% limits of agreement around this mean span from 56 to 151%. This means that for an individual, the two methods can give estimates that differ by 50%. The average agreement between CG and MDRD2 formulas is lower (mean log-difference –0.23) but with smaller variability (48–127%).

Table 1 summarises the agreement of the three methods to classify people as having normal renal function (GFR >60 ml/min/1.73 m^2 BSA), moderate (GFR 30–60 ml/min/1.73 m^2 BSA) and severe (GFR <30 ml/min/1.73 m^2 BSA) renal insufficiency. The MDRD1 and CG formulas are in agreement with 71.2% of cases. The weighted \(\kappa\) is 0.56. The overall agreement between the MDRD2 and the CG formula is poorer, with a \(\kappa\) of 0.44.

Figure 2 shows the difference of the estimate of the GFR obtained using the CG and MDRD1 formulas according to age (panel A), SC (panel B), ratio of actual to ideal...
weight (panel C) and ratio of actual to ideal weight stratified by gender (panel D). The line is drawn using local regression methods smoothing the scatter plot. In younger people, the CG-GFR is higher relative to the MDRD1-GFR, but with increasing age the pattern reverses, with CG-GFR estimates being lower than the MDRD1-GFR estimates. A maximum of discrepancy is seen in people with low creatinine level (<1 mg/ml), but the difference gets smaller for increasing creatinine levels, and is negligible for SC over 2 mg/dl. The degree of discrepancy is strongly influenced by the weight, with the CG-GFR being lower than the MDRD1-GFR in people with lower weight and higher than the MDRD1-GFR in people with higher weight. This pattern indicates an influence of weight on the CG-GFR but not on the MDRD1-GFR. We found similar results stratifying by gender. The results were similar after stratification by diagnosis of HF or diabetes (see supplementary data Appendix 2a and 2b at http://www.ageing.oxfordjournals.org/).

The pattern seen in relation to age, SC and weight of the difference between the CG and the MDRD1 formulas was confirmed using the MDRD2 formula.

When we repeated the analyses using the CG formula corrected for the BSA, the results were consistent, but—as expected—the agreement between the formulas increased: the 95% agreement limits spanned from 66 to 131% (average 93.4%) for the comparison between the CG and the

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| ![Figure 2. Scatter plot of the difference between GFR estimates obtained with the CG and MDRD1 formulas, according to age (A), serum creatinine (B), actual : ideal weight ratio (C) and actual : ideal weight ratio stratified by gender (D).](image)

| <30 (n = 1,093) | 7.7 | 5.3 | 6.2 | 8.2 | 0.1 | 0.6 |
| 30–60 (n = 4,324) | 1.6 | 0.4 | 40.2 | 27.8 | 13.9 | 27.6 |
| >60 (n = 2,330) | 0 | 0 | 6.9 | 1.8 | 23.1 | 28.2 |

Table 1. Agreement of CG-GFR with MDRD1 and MDRD2

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<th>MDRD1-GFR (n = 725)</th>
<th>MDRD2-GFR (n = 439)</th>
<th>MDRD1-GFR (n = 4,136)</th>
<th>MDRD2-GFR (n = 2,928)</th>
<th>MDRD1-GFR (n = 2,886)</th>
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<td>Weighted κ (95% CI)</td>
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MDRD1 estimates and from 58 to 108% (average 79%) for the comparison between the CG and the MDRD2 estimates.

Discussion

Although the CG and MDRD formulas have a good average agreement, at the individual level, the CG formula underestimates the GFR using either of the MDRD formulas as comparison. Our results are in line with others showing that in the elderly population, both the CG and, to a lesser extent, the MDRD formulas tend to underestimate the measured GFR and that age and body mass is an important factor in estimation bias [19]. Therefore, the formulas cannot be used interchangeably to measure renal function in older people [20, 21].

The magnitude of the discrepancy between the CG-GFR and the MDRD1-GFR was strongly influenced by age. Age has a different weight in the two formulas, and its relationship with the GFR is linear in the CG formula and non-linear in the MDRD formulas. However, since we did not directly measure the GFR, we cannot know whether the effect of age is related to a systematic measurement error of one of the two formulas or is because of age-related changes in renal physiology.

Serum creatinine levels are also an important factor influencing the magnitude of the discrepancy between the formulas, and we found the maximum of the discrepancy in the normal range of SC levels. Accordingly, using the MDRD formulas in older people with SC in the normal range would lead to consider having normal renal function a number of people with reduced GFR. However, the difference between the CG-GFR and the MDRD1-GFR is at most 20 ml/min, and the clinical relevance of this difference is debatable.

The CG and MDRD formulas provide quite different estimates of GFR in both underweight and overweight older patients. This finding is unlikely to be biased by overhydration or dehydration, since we referred to the weight measured at discharge, when patients with abnormal water balance had been compensated. Furthermore, the conclusion obtained in the whole population held true after stratification for different diseases. Only 59 of 249 subjects studied by CG were older than 69 years [3], while 55.1% of our patients was over 75. Also, the per cent fat mass was obviously much greater in our population, and the lower the lean mass, the weaker the relationship between weight and muscle protein which is the source of creatinine. At the opposite, extreme malnutrition is frequently associated with a loss of lean more than of fat mass [22]. Thus, being underweight might affect the relationship between weight and CG-derived GFR not much differently from being overweight. Finally, only 4% of patients were studied by CG [3], but 50% of our patients were females. This is likely to increase the variability in the ratio of CG-GFR to MDRD-GFR in overweight females, but it does not affect the main conclusion, because in our study, the differences in the results obtained in men and women were negligible.

The MDRD formulas have been developed in patients with a variety of chronic renal disease [16], and this population differs from that recruited by CG as well as from ours. Chronic renal failure is characterised by loss of muscle mass [23], and subjects having the same age, height and weight might have a quite different body composition depending upon whether renal function is normal or depressed. As a consequence, a formula obtained in a population with chronic renal disease might apply exclusively to that population.

Detecting renal failure in patients with normal SC is important for patient management because depressed GFR is associated with a greater risk of side effects of several drugs [24]. We have shown that the CG and MDRD formulas have the maximum of disagreement in people with low creatinine levels. The CG formula has never been tested among people with normal creatinine levels, and the MDRD formulas have been shown to be not reliable in this population [10, 25]. We think that in these patients, caution must be exercised in basing therapeutic decisions on the GFR estimated with either formula, especially if underweight or overweight are associated. Unfortunately, both malnutrition and obesity are common in older people [26, 27], and direct measurement of GFR should be recommended in a substantial fraction of the older population for whom concealed renal failure would be a health hazard. If logistic problems make the direct measurement of GFR impossible, CG formula should be preferred to the MDRD, provided the estimated GFR helps to monitor the dose of drugs having a narrow therapeutic range and a high potential for ADRs even with mildly depressed renal function.

Both the MDRD formulas do not require weight to be measured, and this can be an advantage in calculating GFR for bedridden patients. While the MDRD2 is more easily calculated than the MDRD1 formula, our data indicate that its agreement with the CG is poorer compared to the MDRD1. If the CG estimate is to be considered in frail patients, then the MDRD1 should be used when information on weight is not available.

Our results should be confirmed in an older population in good health to support the role of weight as the source of discrepancy between the predictive equations independently from the general characteristics of the studied population. However, the lack of effect of co-morbidity and disability on this discrepancy suggests that our results are generalisable to the whole population of older persons. We did not assess the body composition and can only hypothesise that loss of lean mass explains the effect of being underweight or overweight on the degree of concordance between formulas. Our population had a lower prevalence of disability compared to patients who were excluded because of missing data and, therefore, our results might be not generalisable to people with severe disability. The fact that SC was measured by different laboratories might be a source of variability contributing to limit the agreement between formulas. However, all the laboratories complied with a rigorous quality control program, and the formulas should be tested in the daily reality rather than in ideal contexts. Finally, we documented the poor agreement between CG and MDRD formulas but, in the absence of directly measured GFR, we could not assess which of them is more reliable in older people.
In conclusion, we showed that in frail elderly, the CG and MDRD formulas provide quite different estimates of GFR. Efforts should be made to clarify whether one of the two formulas qualifies as more reliable in this population.

Key points

- It is known that creatinine alone is not a reliable marker of renal function, and formulas to calculate the creatinine clearance or the GFR are currently used in clinical practice.
- None of the formulas available have an optimal mix of sensibility and specificity in identifying people with renal failure.
- We showed that there is a noticeable discrepancy between the results yielded by two of the most commonly used formulas (MDRD and CG) in estimating renal function in hospitalised older people.
- The two formulas should not be used interchangeably. Further research is needed to verify which of the two is more reliable in older people.

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References