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Research Article

Accuracy of the methods used to estimate glomerular filtration rate compared to 24-hour urinary creatinine clearance in patients with chronic spinal cord injury

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Objective: To compare the accuracy of glomerular filtration rate (GFR) estimation by 24-hour urinary creatinine clearance with GFR estimation by the Modification of Diet in Renal Disease (MDRD) equation, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, the Mayo Clinic Quadratic equation (MCQE), and the modified Cockcroft–Gault formula in patients with spinal cord injury (SCI).
Design: Cross-sectional study.
Participants: Fifty-nine consecutive subjects, who were admitted to our hospital SCI rehabilitation and no additional acute medical disorders, were enrolled in this study. A 24-hour urine sample was collected for the determination of 24-hour urinary creatinine clearance, which was assumed as the standard technique for estimation of the GFR. The accuracy of several estimation formulas includes the 4-variable MDRD equation, the 6-variable MDRD equation, the Cockcroft and Gault equation, the CKD-EPI equation, and the MCQE.
Results: GFRs calculated by the Cockcroft–Gault equation and 4-variable MDRD were significantly different from the 24-hour urinary creatinine clearance, whereas there were no significant differences in GFRs calculated by CKD-EPI ($P = 1.000$), Mayo Clinic Quadratic formula ($P = 0.794$), and 6-variable MDRD equations ($P = 0.435$) and 24-hour urinary creatinine clearance. Both the 6-variable MDRD equation and CKD-EPI were accurate within ± 20 of the reference methods in 52.54% of the subjects.
Conclusions: Among the methods used for estimation of the GFR including the 4- and 6-variable MDRD, the CKD-EPI, the modified Cockcroft–Gault equation, and the MCQE, the 6-variable MDRD equation and the CKD-EPI demonstrated best performance to estimate the GFR. However, none of the formulas were sufficient to estimate the GFR in SCI patients accurately.

Keywords: Cockcroft–Gault creatinine clearance, Modification of Diet in Renal Disease equation, Chronic Kidney Disease Epidemiology Collaboration equation, Mayo Clinic Quadratic equation, Spinal cord injury, Glomerular filtration rate

Introduction

Patients with spinal cord injury (SCI) are vulnerable to renal deterioration and urinary tract complications, which are reported to constitute the primary cause of death in these patients.[1,2] Patients with SCI should, therefore, have their renal function evaluated regularly. Although glomerular filtration rate (GFR) has been traditionally considered the best measure of renal function, several factors limit the accuracy of the GFR estimation through the creatinine levels in SCI patients.[3] GFR is calculated by the measurement of the plasma clearance rate of agents, such as inulin, iohexol, ^{51}Cr-EDTA, and ^{99m}Tc-DTPA, which are extensively excreted by glomerular filtration.[4] However, the calculation of GFR by these methods is expensive, time-

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consuming, and impractical. Serum creatinine and creatinine clearance are, therefore, commonly used as indirect markers of GFR. However, serum creatinine may be influenced by renal handling and metabolism, food intake, and methodological interference.[5] In addition, serum creatinine levels may be influenced by age, body weight, sex, and ethnicity. On the other hand, protein in serum, glucose, and ketoacids in high levels (diabetic ketoacidosis) may interfere with creatinine assays. Moreover, diffuse muscular atrophy, reduced muscle mass, and prolonged immobility in patients with SCI may complicate the measurement of renal function and overestimate GFR.[6]

Given the relative inaccuracy of GFR calculation by the serum creatinine concentration, several other methods, including the Modification of Diet in Renal Disease (MDRD) equation, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, and the recent Mayo Clinic Quadratic equation (MCQE), have been used to estimate an accurate GFR.[7–9] However, the utility of these formulas in estimating the GFR in patients with SCI has not been tested extensively. Currently, there are only limited data concerning the best method of GFR estimation in patients with SCI.

The purpose of the present study is to compare the accuracy of GFR estimation by 24-hour urinary creatinine clearance with GFR estimation by the MDRD, the CKD-EPI, the MCQE, and the modified Cockcroft–Gault formula in patients with SCI.

Materials and methods

Fifty-nine consecutive subjects, who were admitted to our hospital for SCI rehabilitation and no additional acute medical disorders, were enrolled in this study. Written informed consent was obtained from all subjects. The study was approved by the local ethics committee and was conducted in accordance with the Helsinki declaration. Subjects with limb amputation and with known kidney disease or pathology detected on kidney ultrasonography were excluded. Demographic features and clinical characteristics of the subjects were retrieved from the patient charts and institutional digital database. Admission blood test results were also recorded. A 24-hour urine sample was collected for the determination of 24-hour urinary creatinine clearance, which was assumed as the standard technique for estimation of the GFR. Patients without indwelling catheters were catheterized intermittently. The urine from the catheters was collected. Creatinine clearance was computed from creatinine excretion in a 24-hour urine collection and a single measurement of serum creatinine. The accuracy of several estimation formulas includes the 4-variable MDRD equation, the 6-variable MDRD equation, the Cockcroft and Gault equation, the CKD-EPI equation, and the Mayo Clinic Quadratic equation.

The formulas used to estimate the GFR are as follows:

4-Variable MDRD; $\text{eGFR} = 186 \times \text{standardized serum Cr}^{-1.154} \times \text{age}^{-0.203} \times 1.21 \text{ (if black)} \times 0.742 \text{ (if female)}$;[10–12]

6-Variable MDRD; $\text{eGFR} = 170 \times \text{standardized serum Cr}^{-0.999} \times \text{age}^{-0.176} \times \text{BUN}^{-0.170} \times \text{albumin}^{+0.3189} \times 1.18 \text{ (if black)} \times 0.762 \text{ (if female)}$;[13]

Modified CG formula (CLM) (ml/min) = $[(140-\text{age}) \times \text{ideal body weight in kg}]/(72 \times \text{serum Cr})$; (multiply 0.85 for females); (serum Cr rounded to 1 mg/dl for patients with serum Cr < 1 mg/dl while using the actual serum Cr for patients with serum Cr ≥ 1 mg/dl);[14]

$\text{CKD-EPI} = 141 \times \min(\text{SCr}/k,\ 1)^{\alpha} \times \max(\text{SCr}/k,\ 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018 \text{ (if female)} \times 1.159 \text{ (if black)}$ ($k = 0.7$ for females and 0.9 for males, $\alpha = 0.329$ for females and 0.411 for males);[15]

Mayo Clinic Quadratic formula; $\text{eGFR} = e^{(1.911 + 5.249/\text{serum Cr} - 2.114/\text{serum Cr2} - 0.00686 \times \text{Age} - (0.205 \text{ only if Female}))}$; ($e = 2.71828182845905$).[9]

Glomerular filtration rate and creatinine clearance were expressed per 1.73 m^2 of body surface area by multiplying measured values by 1.73/body surface area.

Statistical analysis

All analyses were performed on SPSS version 21 (SPSS Inc., Chicago, IL, USA) and MedCalc Statistical Software version 15.8 (MedCalc Software bvba, Ostend, Belgium). Q-Q and histogram plots were used to determine whether variables are normally distributed. Data are given as mean ± standard deviation or median (1st quartile–3rd quartile) for continuous variables according to the normality of distribution and as frequency (percentage) for categorical variables. Creatinine clearance and estimated GFR values were analyzed with Friedman's analysis of variance by ranks. Pairwise comparisons were performed with the Bonferroni correction method. The performance of the GFR estimation methods was evaluated with the Bland–Altman analysis and plots. Two-tailed P values of less than 0.05 were considered statistically significant.

Results

The mean age of the study group was 34.36 ± 14.37 (range 16–71) years. Table 1 shows the characteristics and physical examination findings of the participants.

Table 1 Summary of individuals' characteristics and physical examination findings.

Age (years)	30 (24–45)
Sex	
Male	48 (81.36%)
Female	11 (18.64%)
Comorbidities	4 (6.78%)
Diabetes mellitus	4 (6.78%)
Coronary artery disease	2 (3.39%)
Hypertension	3 (5.08%)
Gallbladder stone	1 (1.69%)
Aortic stenosis	1 (1.69%)
Body mass index	22.65 ± 3.34
Duration of cord injury (months)	7 (3–24)
Etiology	
Road accident	25 (42.37%)
Falling down from height	18 (30.51%)
Gunshot injury	5 (8.47%)
Plunge into water	1 (1.69%)
Stay under heavy weight	5 (8.47%)
Transverse myelitis	5 (8.47%)
Spinal injury level	
Cervical	22 (37.28%)
Thoracic	28 (47.45%)
Lumbar	9 (15.25%)
ASIA scale	
A	27 (45.76%)
B	11 (18.64%)
C	12 (20.33%)
D	9 (15.25%)

Data are given as mean ± standard deviation or median (interquartile range) for continuous variables according to the normality of distribution and as frequency (percentage) for categorical variables.

Of all, 6.78% of the study subjects were diabetic and 5.08% were hypertensive. The median duration of the SCI was 7 (3–24) months. The majority of the subjects had a thoracic spinal injury (47.27%). In this study, 52.54% of the subjects were using wheelchair and 37.29% of the study subjects had a constant urinary catheter. On urine analysis, 29.82% of the study subjects had leukocytosis. Intravenous pyelogram and renal ultrasonography were normal in all subjects.

Table 2 demonstrates 24-hour urinary creatinine clearance and estimated GFRs calculated by different formulas. The 24-hour urinary creatinine clearance was ≥90 in 50 (84.74%) of the study subjects. GFRs calculated by the Cockcroft–Gault equation and the 4-variable MDRD were significantly different from the 24-hour urinary creatinine clearance, whereas there were no significant differences in GFRs calculated by the CKD-EPI (P = 1.000), the Mayo Clinic Quadratic formula (P = 0.794), and the 6-variable MDRD equations (P = 0.435), and 24-hour urinary creatinine clearance.

The Bland–Altman analysis results, between creatinine clearance as the gold standard and estimated GFR values, are presented in Table 3. Compared to 24-hour urinary creatinine clearance, all techniques, used to estimate the GFR, exhibited a negative slope (Fig. 1(a–e)). As shown in Table 4, both the 6-variable MDRD equation and the CKD-EPI were accurate within ±20 of the reference method in 52.54% of the subjects.

Discussion

Estimation of the GFR in patients with SCI has been a matter of debate owing to the limitations arising from the altered excretion of the creatinine in this patient population. The 4- and 6-variable MDRD, the CKD-EPI, and the MCQE formulas have been utilized to estimate the GFR in different patient subsets. However, their usefulness in patients with SCI has not been studied yet. The present study purposed to find out the accuracy of GFR estimation through the 4- and 6-variable MDRD, the CKD-EPI, and the MCQE formulas in patients with SCI. Although none of the methods used for estimation of the GFR demonstrated sufficient accuracy, the 6-variable MDRD equation and the CKD-EPI demonstrate best performance to estimate the GFR when the 24-hour urinary creatinine clearance was selected as the reference method for GFR calculation. However, both the 6-variable MDRD equation and the CKD-EPI were accurate within ±20 of the reference method in only 52.54% of the study patients.

Table 2 Summary of creatinine clearance and estimated GFR values.

	Mean ± SD (95.0% CI)	Percentile 5th	25th	50th	75th	95th	P
Creatinine clearance	133.25 ± 44.42 (121.67–144.82)	74.20	98.12	123.21	158.54	230.32	<0.001(1)
Cockcroft–Gault equation	155.42 ± 50.84 (142.17–168.67)	78.52	122.55	151.01	170.83	281.82	<0.001(2)
CKD-EPI	126.02 ± 21.00 (120.55–131.49)	89.90	110.50	128.40	140.80	160.40	1.000(2)
Mayo Clinic Quadratic formula	133.86 ± 15.63 (129.79–137.93)	107.99	120.62	136.36	148.06	156.41	0.794(2)
MDRD-4	154.82 ± 51.26 (141.46–168.18)	87.56	124.86	149.55	173.32	255.11	<0.001(2)
MDRD-6	126.46 ± 37.51 (116.59–136.32)	67.94	101.70	122.52	144.04	211.01	0.435(2)

SD, standard deviation; CI, confidence interval. (1) Friedman's analysis of variance by ranks, (2) Pairwise comparisons (Bonferroni correction method) between creatinine clearance and estimated GFR values.

Table 3 Bland–Altman analysis results between creatinine clearance as gold standard and estimated GFR values.

	Mean difference ± SD (95.0% CI)	P(1)	Limits of agreement		Slope	P(2)
			Lower	Upper		
Cockcroft–Gault equation	22.17 ± 51.57 (8.73–35.61)	0.002	−78.91	123.25	−0.519	<0.001
CKD-EPI	−7.23 ± 39.48 (−17.52–3.06)	0.165	−84.60	70.15	−0.783	<0.001
Mayo Clinic Quadratic formula	0.61 ± 43.37 (−10.69–11.91)	0.914	−84.38	85.61	−0.915	<0.001
MDRD-4	21.57 ± 50.19 (8.49–34.65)	0.002	−76.81	119.95	−0.472	0.001
MDRD-6	−7.55 ± 40.48 (−18.19–3.09)	0.161	−86.88	71.78	−0.559	<0.001

Positive values represent higher estimates and negative values represent lower estimates than actual GFR values. SD, standard deviation; CI, confidence interval. (1) P values were obtained for H_0: mean difference = 0 hypothesis and (2) P values for slope.

Patients with SCI have been subject to a number of studies to investigate the best formula for estimating the GFR. It was previously stated by Levey *et al.* that creatinine-based equations have critical limitations in patients with extremely low muscle mass.[7] Therefore, it has been reported that creatinine-based equations would result in considerable overestimation of GFR and serum creatinine levels are not able to detect the early stages of renal deterioration in SCI patients.[16]

Previous data have shown that endogenous creatinine clearance, measured on appropriately collected urine samples, was accurate enough for the determination of the GFR in patients with SCI.[17] However, it is time-consuming and impractical to calculate GFR from urine samples collected for 24 hours.

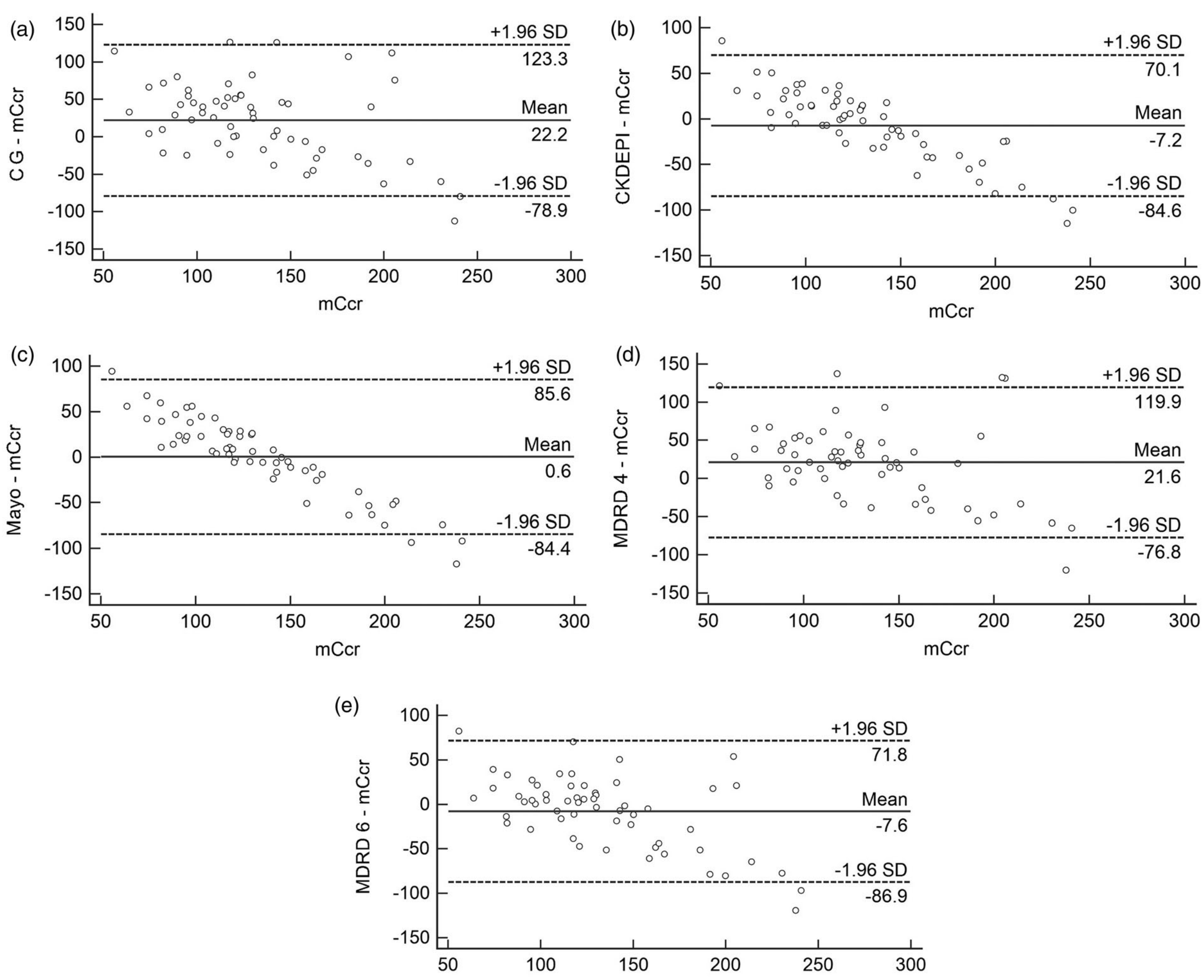

Figure 1 Bland–Altman analysis results between creatinine clearance as gold standard and estimated GFR values. (a) the Cockcroft–Gault equation, (b) the CKD-EPI, (c) the Mayo Clinic Quadratic formula, (d) the MDRD-4, and (e) the MDRD-6.

Table 4 Differences (percentage) between creatinine clearance and estimated GFR values.

	Mean ± SD (95.0% CI)	Percentile					Within ±20.0%
		5th	25th	50th	75th	95th	
Cockcroft–Gault equation	24.13 ± 44.18 (12.61–35.64)	−32.00	−12.51	23.82	46.81	89.97	18 (30.51%)
CKD-EPI	2.84 ± 33.05 (−5.78–11.45)	−40.85	−21.85	−0.38	16.31	62.01	31 (52.54%)
Mayo Clinic Quadratic formula	10.94 ± 38.15 (0.99–20.88)	−38.06	−11.38	5.78	24.22	87.82	27 (45.76%)
MDRD-4	23.36 ± 43.03 (12.15–34.57)	−28.07	−7.42	19.70	46.31	88.25	20 (33.90%)
MDRD-6	−0.04 ± 32.18 (−8.51–8.42)	−40.14	−26.68	1.35	11.25	53.21	31 (52.54%)

Positive values represent higher estimates and negative values represent lower estimates than actual GFR values. SD, standard deviation; CI, confidence interval.

Therefore, whether the performance of several formulas used for the estimation of the GFR in general population could provide similar accuracy in SCI patients is under research. The Cockcroft–Gault equation, which has provided promising results for estimating the GFR in several patient subsets, has been proposed to overestimate the GFR by about 30% in patients with chronic SCI at all stages of chronic kidney disease, particularly in quadriplegic subjects.[6] However, an empirically derived correction factor of 0.8 for the Cockcroft–Gault equation led to a significant improvement in accurate determination of the GFR in SCI patients.[6] Similar to the Cockcroft–Gault equation, the MDRD formula overestimates the GFR by about 40% in patients with SCI. A correction factor of 0.7 for the estimation of the GFR by the MDRD formula improves the accuracy of the formula in SCI patients.[18] Due to problems with changes in creatinine production and secretion, other endogenous compounds have been evaluated. Cystatin C is one of them. Unlike creatinine, Cystatin C is not affected by body muscle mass. However, serum Cystatin C concentration may be elevated by hypothyroidism, steroid use, and rheumatoid arthritis and may be reduced by hyperthyroidism. Moreover, the test is neither widely used nor easily available at this time and is costlier compared to serum creatinine. A few studies have also investigated the performance of serum Cystatin C levels for the estimation of the GFR in patients with SCI. The study of Erlandsen *et al.*, which used a novel equation based on a single serum Cystatin C value, has revealed that this formula could accurately estimate the GFR in patients with SCI regardless of age, sex, and muscle mass.[18] This finding confirmed the results of the study of Jenkins *et al.*, in which serum Cystatin C was a convenient and more reliable surrogate marker of GFR than serum creatinine in patients with SCI.[19] Nevertheless, data are lacking concerning the role of the Mayo Clinic Quadratic formula, the modified Cockcroft–Gault formula, and the CKD-EPI for the estimation of the GFR in patients with SCI.

In this study, we compared the performance of a number of formulas for the estimation of the GFR in SCI patients. Although none of the formulas, including the 4- and 6-variable MDRD, the CKD-EPI, the modified Cockcroft–Gault equation, and the MCQE, were sufficient to estimate GFR and early renal insufficiency in patients with SCI, the 6-variable MDRD equation and the CKD-EPI estimated the GFR accurately within ±20 of the reference method in 52.54% of the patients with SCI. Our findings indicate that patients with SCI constitute a specialized group in which the detection of early renal damage is complicated by the use of the aforementioned formulas. Novel research with a larger sample size may improve our attempts to find the most accurate method for the estimation of the GFR in this special patient population.

The lack of a gold standard technique for evaluating the renal function, such as nuclear scintigraphy, is a major limitation for this study. However, nuclear techniques are time-consuming, expensive, and impractical for the evaluation of the renal function in such a study population. Given that renal function evaluation based on creatinine clearance is readily available, simple, and cost-effective, we used creatinine clearance as a standardized test.

Conclusion

Among the methods used for the estimation of the GFR, including the 4- and 6-variable MDRD, the CKD-EPI, modified Cockcroft–Gault equation, and the MCQE, the 6-variable MDRD equation, and the CKD-EPI, demonstrated best performance. However, none of the formulas were sufficient to estimate the GFR in SCI patients accurately. Further research is required to seek a more accurate method for estimating GFR.

Disclaimer statements

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Conflicts of interest Authors have no conflict of interests to declare.

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