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PAPER

Estimation of glomerular filtration rate in patients with systemic lupus erythematosus

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The objective of this study was to compare the limit of agreement of creatinine clearance (CrCl) estimated by different equations with the CrCl measured by 24-hour urine collection in Hong Kong Chinese patients with systemic lupus erythematosus (SLE). Forty-three SLE patients with mild to moderate renal impairment (serum creatinine concentration $>80\,\mu mol/L$ to $<300\,\mu mol/L$ for females; and $>106\,\mu mol/L$ to $<300\,\mu mol/L$ for males) and not requiring renal replacement therapy were assessed. The estimated clearances were calculated by the Cockcroft-Gault (CG) equation, the Modification of Diet in Renal Disease (MDRD) study equation and the abbreviated MDRD (aMDRD) study equation. The estimated clearances were compared against the measured CrCl by 24-hour urine collection for their limit of agreement. Forty-three patients with mean ($\pm$SD) age of 41.6 ($\pm$8.4) years were assessed. As compared to the measured CrCl in patients with SLE, the clearances by CG equation, MDRD and aMDRD equations predicted a mean difference of -0.8% (95% confidence interval, -43.9–42.3%); -8.6% (95% CI, -24.3–7.2%) and -4.7% (95% CI, -21.4–12%), respectively. There is a tendency for the MDRD and aMDRD study equations to underestimate CrCl. The MDRD and aMDRD study equations have better predictive value than the CG equation. *Lupus* (2006) **15**, 276–281.

Key words: Cockcroft-Gault formula; GFR prediction equations; glomerular filtration rate; MDRD study equations; systemic lupus erythematosus

Introduction

Renal involvement has been the most important determinant of both morbidity and mortality in systemic lupus erythematosus (SLE).[1] Although the survival of SLE has improved dramatically over the past decade, cumulative renal damage results in increased morbidity.[1,2] Chronic renal impairment is an index of damage. Early renal damage predicts renal failure.[3,4] While SLE is associated with atherosclerosis, chronic renal impairment is also found to be an independent risk factor for cardiovascular risk and all-cost mortality in recent studies.[5,6] Accurate and convenient measurement of renal function has an important bearing on the clinical management, risk stratification and medication dosage adjustment among patients with SLE.

Determination of glomerular filtration rate (GFR) by inulin or radioisotopes is not practical in daily practice and serum creatinine concentration is far from a good surrogate marker. Chromium-51 ethylenediamine tetraacetic acid GFR (^{51}Cr-EDTA) was proposed as being the gold standard for yearly measure of GFR in SLE patients.[7] However, it is costly, involves the use of radioactive substances and is not available routinely in our setting. Creatinine clearance (CrCl) approximates GFR but overestimates it due to the fact that creatinine is secreted in the proximal tubule. Calculation of CrCl by 24-hour urine collection is commonly adopted as an estimate of GFR. However, it is frequently inaccurate and inconvenient, especially among the young working class. Since its introduction in 1976, the Cockcroft-Gault (CG) equation has been widely adopted for the estimation of CrCl in adults.[8] As it is the case with CrCl, CG equation tends to overestimated GFR. In 1999, the Modification of Diet in Renal Disease (MDRD) study group proposed a new equation for estimation of GFR.[9] This equation was derived from 1628 subjects with renal insufficiency. The primary aim of the initial study was to show restricting protein intake and controlling blood pressure can delay the progression of renal disease.[10]

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An abbreviated Modification of Diet in Renal Disease (aMDRD) study equation was published in 2000.[11] It estimates the GFR based on serum creatinine concentration, age, sex and race. On average, GFR estimated from the MDRD Study equations are more accurate than measured CrCl or CrCl estimated by the CG equation in patients with reduced GFR. The National Kidney Foundation (NKF) and American Society of Nephrology (ASN) recommend the aMDRD study equation for the estimation of GFR.[12] The MDRD study equations have been evaluated in diabetic and non-diabetic patients with chronic kidney disease, potential renal transplant donors with CrCl <80 mL/min and scleroderma patients.[13–15] There is no published study to compare the MDRD study equations among SLE patients up to the time of writing. This is a study to compare the estimated GFR by different equations with measured CrCl by 24-hour urine collection in Hong Kong Chinese patients with SLE.

Objectives

This cross-sectional study aims at comparing the estimated CrCl by different equations against the CrCl derived from 24-hour urine collection. The estimation equations were the CG equation, MDRD and aMDRD study equations.[8,9,11] The CG equation estimates the CrCl while the MDRD study equations estimate the GFR using demographic and serum variables. The limit of agreement of the estimated clearance was represented by the absolute difference and percentage absolute difference.

Methods

Patients with SLE were recruited from rheumatology outpatient clinics in two regional hospitals in Hong Kong. Subjects with mild to moderate renal impairment (serum creatinine concentration >80 μmol/L to <300 μmol/L for females; and >106 μmol/L to <300 μmol/L for males) and not requiring renal replacement therapy were identified. These subjects were 18 to 65 years old. All fulfilled the 1982 American College of Rheumatology revised criteria for SLE.[16] Demographic data were collected, including age, sex, body weight and height. Body weight was measured to the nearest 0.1 kg by a standard bean balance. Body height was measured to the nearest 0.5 cm without shoes. The total body surface area (TBSA) was calculated by the DuBois and DuBois formula.[17] A 24-hour urine collection was used for the calculation of CrCl. Blood tests for renal function, liver function, complete blood picture, erythrocytes sedimentation rate, serum complement, anti-double stranded DNA were taken on the day they completed 24-hour urine collection. Serum creatinine concentrations were assayed using the Jaffe total chromagen method (Kreatinine Methode Jaffe, Hitachi 717, Boehringer Mannheim, Germany). SLE disease activities were assessed by systemic lupus erythematosus disease activity index (SLEDAI) within 10 days before or after urine collection. Subjects with extremes of age and body size; paraplegia; or those with myositis; or on vegetarian diet; or those taking cimetidine, trimethoprim, fibric acid derivatives and cephalosporins were excluded from study. Subjects who had incomplete urinary collection were also excluded.[12] Incomplete urinary collection was defined as a 24-hour urine volume less than 1.2 L or urine creatinine less than 7 mmol/day. The estimated CrCl/ GFR were calculated by the CG equation (CG clearance), the MDRD study equation (MDRD clearance) and the aMDRD study equation (aMDRD clearance). The CrCl by 24-hour urine collection was used as the reference against which the estimated clearances were compared. The MDRD and the aMDRD study equations give the estimated clearances per 1.73 m^2, while the measured CrCl and estimated CG clearance are not adjusted to TBSA. The measured CrCl and CG clearance were thus standardized for comparison by a multiplication of 1.73/TBSA (Table 1). As recommended by the National Kidney Foundation, a predefined limit of agreement is ideally between $\pm 10\%$. Description of the percent of estimates falling within 30% and 50% above or below the measured GFR is a useful measure of accuracy.[12]

Table 1 Estimation equations

Conventional Creatinine clearance derived from 24-hour urine collection (standardized to total body surface area 1.73 m^2)

CrCl (standardized) = Ucr × Vol/Pcr × 0.011/1440 × (1.73/TBSA)

Cockcroft-Gault Equation (standardized to total body surface area 1.73 m^2)[5]

CrCl = 140-age (years) × BW(kg)/ 72 × Pcr × 0.011 × correctional factor × (1.73/TBSA) *Females: correctional factor (0.85)*

Modification Diet in Renal Disease study Equation[6]

GFR = 170 × Pcr × $0.011^{-0.999}$ × $Age^{-0.176}$ × 0.762 if patient is female × 1.180 if patient is black × $SUN^{*-0.170}$ × Alb × $0.1^{+0.318}$

Abbreviated Modification Diet Renal Disease study Equation[7]

GFR = 180 × Pcr × $0.011^{-1.154}$ × $Age^{-0.203}$ × 0.742 if patient is female × 1.210 if patient is black

Total body surface area (TBSA) by the DuBois and DuBois Formula[15]

TBSA = ($BW^{0.425}$ × $BH^{0.725}$) × 0.007184

GFR: Glomerular filtration rate (mL/min per 1.73 m^2); Alb: serum alb concentration (g/L); Pcr: serum creatinine concentration (μmol/L); BW: body weight; SUN: serum urea nitrogen concentration (mmol/L), *SUN in mg/dL = urea concentration in mmol/L × (1/0.357); Vol: volume of urine; collection over 1440 min in mL; TBSA: total body surface area in m^2; BH: body height.

Statistical analysis

The statistical analysis was done by the Statistical Package for Social Science (Windows version 12, SPSS Inc., Chicago, USA). The limits of agreement between the measured CrCl and estimated GFR/CrCl by different equations were analysed by the Bland and Altman Method,[18] using the Med Calc statistical software version 7.6.0 (demo version). This method depicts the mean difference and 95% confidence interval of the difference, the limit of agreement (mean difference ± 1.96 SD). The rank correlation between the absolute differences and the means were presented. The median and percentile absolute differences (2.5th, 25th, 50th, 75th, 97.5th) between the estimated CrCl/GFR and measured CrCl were also presented for comparison.

Results

Forty-nine subjects fulfilling the inclusion criteria were identified and 43 were finally assessed. Six subjects were excluded: one for tetraplegia; one for refusal to have 24-hour urine collection and four for grossly incomplete urinary collection. Forty-three subjects participated in this study, including 42 female and one male with mean (±SD) age of 41.6 (±8.4) years. The mean (±SD) body weight, height, body mass index and total body surface area were 40.4 (±11.1) kg, 156.9 (±7.7) cm, 22.3 (±3.8) and 1.54 (±0.17) m^2. The mean creatinine was 146.5 (±66.8) μmol/L. The mean (±SD) measured CrCl by 24-hour urine collection was 47.4 (±19.3). The mean (±SD) estimated CrCl/GFR by the CG, MDRD and aMDRD study equations were 46.7 (±18.1), 43.4 (±17.9) and 44.8 (±17.3) mL/min/1.73 m^2, respectively (Table 2). Only 4.7% of subjects were currently taking cyclophosphamide. Majority were taking low doses of prednisolone, mean daily dose was only 6.5 mg (0–20 mg), which would not affect the creatinine or urea excretion. There is no correlation between dosage of prednisolone, disease activities, degree of proteinuria or WHO nephritis class and the percentage difference of clearances (Table 3).

The absolute (and percentage) median differences of the CG clearance, MDRD clearance, aMDRD clearance in comparison to measured CrCl were −0.4 mL/min/1.73 m^2 (−0.66%), −2.8 mL/min/1.73 m^2 (−7.75%) and −1.2 mL/min/1.73 m^2 (−4.13%) respectively (Table 4). This implies a tendency for the MDRD and aMDRD study equations to underestimate CrCl in our studied subjects.

The limit of agreement between the estimated CrCl/GFR and measured CrCl were analysed by the Bland and Altman method. The mean difference provides information on the accuracy or bias; and the limits of agreement are shown on a simple plot (Figures 1–3). For the CG clearance, the mean difference was −0.7 mL/min/1.73 m^2 (95% confidence

Table 2 Demographical and clinical data

Characteristics	*Percentage*	*Mean ± SD*	*Median*	*Range*
Age (year)	—	41.6 ± 8.4	41.0	24–64
Body height (cm)	—	156.9 ± 7.7	156.0	140–178
Body weight (kg)	—	54.6 ± 11.1	51.9	40.5–97.5
BMI	—	22.3 ± 3.8	22.2	16.2–35.1
TBSA (m^2)	—	1.54 ± 0.17	1.51	1.30–2.20
SLEDAI	—	6 ± 3.49	6	0–12
Currently medications:				
Cyclophosphamide	4.7	—	—	—
MMF	7	—	—	—
Azathioprine	37.2	—	—	—
Hydroxychloroquine	34.9	—	—	—
Other immunosuppressants	9.3	—	—	—
Prednisolone	95.3	–	—	—
Dose of prednisolone (mg/day)	—	6.5 ± 4.1	5.0	0–20
Serum Cr (μmol/L)	—	146.5 ± 66.8	117	81–298
Serum albumin (g/L)	—	38.09 ± 4.48	39	24–47
24-hour urine total protein (g/day)	—	1.3 ± 1.8	0.7	0.08–9.0
sCrCl (/min per 1.73 m^2)	—	47.4 ± 19.3	47.1	15.0–80.1
sCG clearance (/min per 1.73 m^2)	—	46.7 ± 18.1	53.1	12–82.6
MDRD clearance (/min per 1.73 m^2)	—	43.5 ± 17.9	43.3	14.2–77.1
aMDRD clearance (/min per 1.73 m^2)	—	44.8 ± 17.3	47.1	14.8–73.6

BMI: body mass index; TBSA: total body surface area; SLEDAI: systemic lupus erythematosus disease activity index; MMF: mycofenolate mofetil; sCrCl: standardized creatinine clearance; sCG; standardized Cockcroft-Gault equation; MDRD: Modification of Diet in Renal Disease study equation; aMDRD: abbreviated Modification of Diet in Renal Disease study equation.

Table 3 Correlation between the percentage differences of different clearances and disease activities

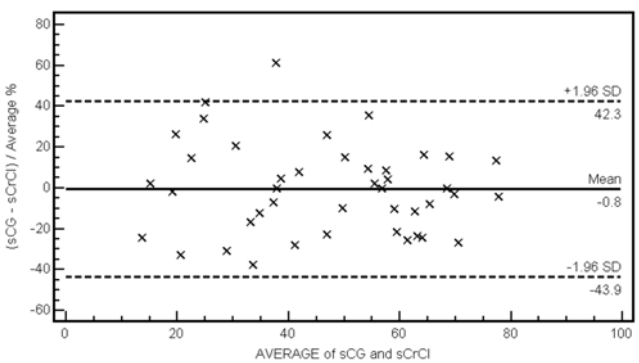
	Percentage difference of sGC clearance	*Percentage difference of MDRD clearance*	*Percentage difference of aMDRD clearance*
SLEDAI	−0.2206 $P = 0.1551$	−0.1319 $P = 0.3990$	−0.0104 $P = 0.9472$
Dose of prednisolone	0.2365 $P = 0.1267$	0.0287 $P = 0.8549$	0.1167 $P = 0.4561$
WHO nephritis class	0.029 $P = 0.8575$	−0.079 $P = 0.6206$	−0.036 $P = 0.8244$
Degree of proteinuria	0.060 $P = 0.704$	0.083 $P = 0.596$	0.244 $P = 0.114$

SLEDAI: systemic lupus erythematosus disease activity index; sCrCl: standardized creatinine clearance; sCG; standardized Cockcroft-Gault equation; MDRD: Modification of Diet in Renal Disease study equation; aMDRD: abbreviated Modification of Diet in Renal Disease study equation.

Table 4 Absolute and percentage difference among estimated clearances and the measured CrCl

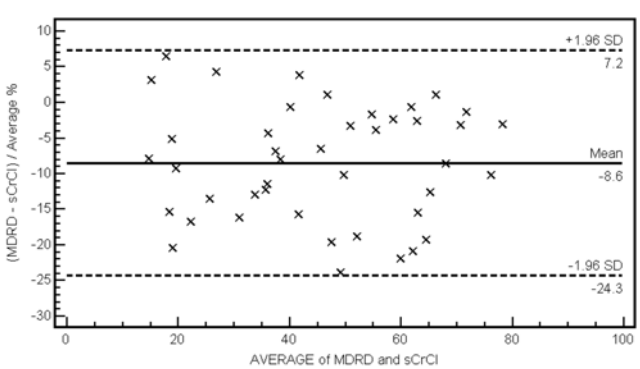
Estimated clearances	*sCG (%)*	*MDRD (%)*	*aMDRD (%)*
Mean	−0.7	−3.9	−2.6
Median	−0.4 (−0.66)	−2.8 (−7.75)	−1.2 (−4.13)
Percentiles: 2.5	−18.7 (−31.4)	−13.2 (−21.2)	−11.3 (−19.5)
25	−6.9 (−19.6)	−5.9 (−14.4)	−6.0 (−11.4)
50	−0.4 (−0.66)	−2.8 (−7.75)	−1.2 (−4.13)
75	5.1 (15.76)	−1.0 (−2.7)	0.3 (0.0)
97.5	22.7 (84.08)	−1.6 (10.3)	5.6 (13.7)

sCG: standardized Cockcroft-Gault equation; MDRD: Modification of Diet in Renal Disease study equation; aMDRD: abbreviated Modification of Diet in Renal Disease study equation.



sCG: standardized Cockcroft-Gault clearance; CrCl: Creatinine clearance.

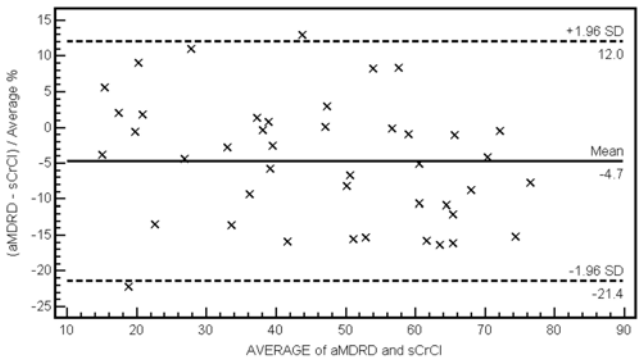
Figure 1 Bland and Altman plot of the clearance estimated by CG equation.



MDRD: Modification of Diet in Renal Disease study clearance; CrCl: creatinine clearance.

Figure 2 Bland and Altman plot of the clearance estimated by MDRD equation.

interval: −19.3 to 17.8 mL/min/1.73 m^2), meaning that the estimated CrCl might differ from 43.9% below and 42.3% above the measured CrCl. For the MDRD and aMDRD clearances, the mean differences were −3.9 mL/min/ 1.73 m^2 (95% confidence interval: −11.8



aMDRD: abbreviated Modification of Diet in Renal Disease study clearance; CrCl: creatinine clearance.

Figure 3 Bland and Altman plot of the clearance estimated by aMDRD equation.

to 4.0 mL/min/1.73 m^2) and −2.6 mL/min/1.73 m^2 (95% confidence interval: −10.9 to 5.8 mL/min/ 1.73 m^2). The MDRD clearance might differ from 24.3% below and 7.2% above the measured CrCl. The aMDRD clearance might differ from the measured CrCl from 21.4% below and 12% above.

As recommended by the National Kidney Foundation, a predefined limit of agreement is ideal if it is between ±10%, while it is a useful measure of accuracy when the limit of agreement falls within 30% and 50% above or below the measured GFR. Hence, all the estimated CrCl/GFR by different equations were not ideal, but were all clinically accurate. As compared to the CG equation, the MDRD and aMDRD study equations were more accurate. The MDRD equations are better predictors in our studied subjects.

Discussion

Good estimation of renal function is an essential part in the day-to-day management of patients with SLE. Accurate measurement of renal function is required for monitoring disease activity and cumulative renal damage. It may also be a marker of increased cardiovascular risk. However, the serum creatinine concentration is not a good surrogate marker of GFR. Serum creatinine concentration is affected by other factors, such as tubular generation, secretion and extra renal excretion of creatinine. The extra-renal creatinine excretion is increased in patients with chronic kidney disease due to the degradation of creatinine by bacterial overgrowth in the small bowel. As much as two-thirds of total daily creatinine excretion can occur by extra-renal creatinine elimination in patients with severely reduced kidney function. As a consequence, urinary creatinine excretion is lower in chronic kidney

disease, leading to systematic overestimation of GFR from serum creatinine. Moreover, GFR must decline to approximately half the normal level before the serum creatinine concentration rises above the upper limit of normal. Inulin clearance is widely regarded as the gold standard for measuring GFR. It requires an intravenous infusion and timed urine collections over a period of several hours making it costly and cumbersome. Plasma clearance of exogenous substances like ^{51}Cr-EDTA has been used. However, it is costly, requires the use of radioisotopes and is not routinely available in our hospital. Calculation of CrCl by 24-hour urine collection is commonly used. Estimation of GFR using equations based on serum creatinine concentration is more convenient. The CG and the MDRD study equations are the most widely used equations for the estimation of CrCl/GFR. The aMDRD study equation is the recommended method for estimation of GFR by the National Kidney Foundation (NKF) and American Society of Nephrology (ASN).[12]

In our study, the subjects were Hong Kong Chinese patients with SLE recruited from two regional hospital outpatient specialist clinics. They were from 24 to 64 years old, ambulatory subjects with mild to moderate renal insufficiency, and not requiring renal replacement therapy. This study highlighted several problems of 24-hour urine collection. First, incomplete urine collections are not uncommon even among young populations. Second, a 24-hour urine collection is very inconvenient especially among the working class.

The major limitation of our study is that there is no gold standard of measurement of GFR against which the equations were compared with. The subjects included in our study have mild to moderate renal impairment as defined by a serum creatinine concentration of $>$80–300 μmol/L for females; and $>$106–$<$300 μmol/L for males and not requiring renal replacement therapy. The result should not be generalized to all patients with SLE especially those with normal serum creatinine concentration. Similar studies in adults without kidney disease revealed that the MDRD study equations consistently underestimated while the CG equation consistently overestimated GFR.[19,20]

As compared to the measured CrCl by 24-hour urine collection, we find that the CG, MDRD and aMDRD clearances did not fall into the ideal predefined limit of agreement (±10%). However, they were all clinically accurate as the limit of agreement falls within 30% and 50% above or below the measured GFR. The GFR estimated by the MDRD and aMDRD study equations tend to be more accurate. Accuracy combines precision and bias. Precision expresses the variability (or dispersion) of prediction equation estimates around the reference GFR measure. There is lesser variability of the MDRD clearances around the reference CrCl as compared to the CG equation, making them more precise in estimating GFR. No significant difference between the estimated GFR by the MDRD and aMDRD study equations was found. There is a tendency for the MDRD study equations to underestimate the CrCl. As the measured CrCl tends to overestimate GFR, this 'underestimation' of CrCl by the MDRD study equations observed in our study may mean that they are more accurate for the estimation of GFR.

The Cockcroft-Gault equation was developed to predict CrCl rather than GFR. As creatinine is secreted in renal tubules, CrCl by 24-hour urinary collection and its estimation equations would overestimate GFR. Overestimation of GFR by CG equation among subjects without kidney disease was reported in previous studies.[19,20] In our study, we are using the CrCl by 24-hour urinary collection as reference rather than GFR. The GC equation did not over- or underestimates CrCl in this study. However, there is a great variability of the CG clearances around the reference GFR measure making it less accurate than the MDRD equations.

In this study, GFR estimated by the MDRD study equations were more accurate. These methods are also more convenient and easy to use. Previous study revealed that serial measurement of CrCl did not accurately measure the magnitude of change in GFR in lupus nephropathy.[21] The GFR estimated by MDRD study equations may be a better marker in serial monitoring of renal function. The use of serum Cystatin C is another option to consider in estimation of GFR. Whether these equations may also serve as a surrogate marker for cardiovascular risk warrant further studies.

Conclusion

As compared to the measured CrCl by 24-hour urine collection, there is a tendency for the MDRD study equations to underestimate the CrCl in patients with SLE and having mild to moderate renal impairment. All the estimation equations do not agree with the measured CrCl according to ideal predefined limit of agreement (±10%). All the estimation equations are clinically accurate. The MDRD study equations seem to be more accurate.

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