Bedside Renal Assessment: A Comparison of Various Prediction Equations in Thai Healthy Adults

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Objectives: *To compare the performance of various prediction equations for creatinine clearance (CrCl) and glomerular filtration rate (GFR) estimation in healthy Thai adults.*
Material and Method: *60 healthy adults had urine analysis, serum creatinine and 24-hour urinary creatinine assessment. The author compared Cockcroft-Gault (CG), MDRD, and Rule equations, and that using urine-CrCl for estimation of GFR.*
Results: *The urine-CrCl was 105.3 39.3 ml/min/1.73 m^2. The CrCl/GFR using CG and MDRD equations were significantly lower than urine-CrCl. There was considerable difference between the stratification of renal function with the various formulae. According to both equations, the incidence of subjects with CrCl/GFR of < 90 ml/min/1.73 m^2 was about 60%. R^2 reflecting the degree of correlation between estimated CrCl/GFR and the urine-CrCl was weak.*
Conclusion: *The performance of the CG and MDRD equations were suboptimal for renal function assessment in Thai healthy adults. Further research is required to develop more reliable methods for estimating GFR across different ethic groups.*

Keywords: *Glomerular filtration rate, Creatinine clearance, Prediction equations, Normal healthy Thai adults, Cockcroft-Gault equation, MDRD equation*

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There are considerable benefits from appropriate management of patients with mild chronic kidney disease (CKD). This task can be achieved by accurate and reliable renal function assessment. Glomerular filtration rate (GFR), determined by inulin or radioisotope studies, is widely considered as the best way to evaluate renal function. Unfortunately, this method is impractical to perform and available in only a small number of hospitals. To circumvent this problem, a number of predictive equations have been developed for a bedside assessment of GFR[1].

The recent Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines[2] advocate use of the formulae proposed by either Cockcroft and Gault (CG)[3] or the Modification of Diet in Renal Disease (MDRD) equations to predict GFR in adults[4,5]. Most clinicians throughout the world, including Thailand, utilize them to identify and stratify patients at risk of renal disease. The author also used these equations to estimate GFR in individuals who had normal Serum creatinine (Scr) level for certain situations such as in evaluating living kidney donors. However, several recent studies showed that both equations were much less accurate and precise in those who are otherwise healthy with normal Scr levels[6-13]. Furthermore, both equations were derived primarily from a Caucasian population thus it may not be directly applicable to other racial groups. The validity of these prediction equations need to be tested before their application in clinical practice in Thai people.

The aim of the present study was to compare the estimated creatinine clearance (CrCl)/GFR using various prediction formulae including CG and MDRD equations with 24-hour urine CrCl in healthy adults without renal disease. In the present study the author used urine CrCl rather than inulin clearance as a reference. It was because established standard methods for estimation of GFR (e.g. inulin clearance, radio-isotope

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methods) were not available at the study center and a previous study has shown that the urine CrCl is an excellent measure of GFR in normal subjects[14]. It is frequently used as a tool for evaluating renal function in potential kidney donors. The author hypothesizes that the use of the MDRD and CG equations to assess GFR may not be optimal in healthy subjects of Thai origin.

Material and Method

Healthy subjects and serum creatinine assays

Healthy adults of Thai origin were recruited from the local population at Songkhla, Thailand. They underwent evaluation, including urine analysis, Scr and 24-hour urine creatinine (Ucr) estimation. All subjects were on a regular diet. The participants performed only one outpatient urine collection to determine the urine CrCl. Overnight-fasting blood was drawn after 24-hour urine collection. Scr and Ucr levels were measured by the modified kinetic Jaffe reaction using a Konelab 60 analyzer (Thermo Electron Corporation, Waltham, MA, USA) that was calibrated daily. Subjects who had a history of primary or secondary renal disease, hypertension, chronic obstructive pulmonary disease, and liver disease did not enroll in the present study. Individuals who exhibited Scr > 1.4 mg/dl, positive urine protein on dipstick, or aged less than 18 years or more than 60 years, body mass index $\geq$ 30 kg/m^2 and pregnant state were excluded from the present study. Subjects who had taken cimetidine or diuretics were also excluded. All participants gave informed written consent. The study protocol was approved by the hospital ethics committee of Hat-Yai Hospital, Songkhla, Thailand.

Calculation

24-hour urine CrCl was calculated by standard equation (equation 1). To account for difference in body size, all CrCl were standardized for a body surface area (BSA) that was estimated by DuBois and DuBois' formula[15] (equation 5) using standard height of 1.73 m^2. Estimated GFR equations were adjusted for BSA and displayed as ml/min per 1.73 m^2. The prediction equations for CrCl/GFR were listed as follows:

1. Urine CrCl = Ucr volume urine 1.73 / (Scr BSA 100)
2. Cockcroft-Gault[3]: CrCl-CG = [(140 – age) BW] (0.85 in female) 1.73 / (Scr 72 BSA)
3. MDRD[5]: GFR-MDRD = 186 [Scr]$^{-1.154}$ [age]$^{-0.203}$ (0.742 in female) (1.212 in black)
4. Rule[10]: GFR-R = 224 Scr $^{-1.190}$ age $^{-0.236}$(0.796 in female) (1.26 in healthy)
5. BSA[15] = 0.007184 height$^{0.725}$ weight$^{0.425}$
6. The mean differences = urine CrCl – estimated CrCl/GFR

NB: CrCl, creatinine clearance (ml/min per 1.73 m^2); Ucr, urine creatinine (mg/dl); Scr, serum creatinine (mg/dl); BSA, body surface area (m^2); CG, Cockcroft and Gault; age, in year; BW, body weight (kg); MDRD, Modification of Diet in Renal Disease; GFR, glomerular filtration rate; height, in cm.

Statistical analysis

Data were expressed in mean values $\pm$ SD. The differences between the estimated CrCl/GFR and urine CrCl were analyzed by the paired Student's *t*-test or Wilcoxon rank sum test where appropriate. The degree of correlation and coefficient of determination (R^2) between estimated CrCl/GFR and the urine CrCl was determined by R^2 of linear regression. The author also analyzed separately subjects with proper urine collection, defined as 24-hour Ucr excretion (Ucr urine volume/body weight) was 15-20, 20-25 mg/kg in female, male respectively.

Results

Sixty healthy subjects participated in the present study (30 males and 30 females). Table 1 shows the characteristics of the study population. The mean age was 39 $\pm$ 11 years (range, 19-58). Mean Scr was 0.95 $\pm$ 0.20 mg/dl (range, 0.50-1.40). Mean urine CrCl was 105.3 $\pm$ 39.3 ml/min per 1.73 m^2 (range, 53.66-291.20). BSA, Scr, and Ucr excretion were higher in male subjects (Table 1), but urine CrCl was comparable between the genders.

Table 2 summarizes comparison between estimated GFR/CrCl and urine CrCl. The urine CrCl was significantly higher than CrCl-CG, and GFR-MDRD, but it was lower than predicted GFR proposed by Rule[10]. The R^2 between urine CrCl and all estimated CrCl/GFR was comparable, but poor. The mean GFR by various methods and that by urine CrCl were not significantly different between total and proper urine collection groups. All relationships were much improved when only subjects with proper urine collection were analyzed.

Table 2 also shows that the urine CrCl of 22 (36.7%) healthy persons was less than 90 ml/min per 1.73 m^2, so-called mild renal impairment. Based on the CrCl-CG and GFR-MDRD, the incidence of subjects with mild renal impairment was high (56.7, 66.7%, re-

Table 1. Clinical characteristics of study group

Characteristics	Male (n = 30)	Female (n = 30)	Total (n = 60)
Age, year	39 ± 11	40 ± 11	39 ± 11
Height, cm	166.9 ± 6.0	154.9 ± 6.1*	160.9 ± 8.5
Weight, kg	66.1 ± 8.9	52.7 ± 12.0*	59.4 ± 12.4
Body mass index, kg/m^2	23.61 ± 2.33	22.67 ± 2.99	23.14 ± 2.70
Body surface area, m^2	1.74 ± 0.14	1.52 ± 0.12*	1.63 ± 0.17
Serum creatinine, mg/dl	1.08 ± 0.16	0.81 ± 0.12*	0.95 ± 0.20
Urine creatinine excretion, mg/kg	22.4 ± 4.2	18.6 ± 7.2*	20.5 ± 6.1
Urine CrCl, ml/min/1.73 m^2	95.4 ± 20.9	115.3 ± 50.1	105.3 ± 39.3

* $p < 0.05$; compared males vs female

Table 2. Mean CrCl/GFR, mean difference, correlation, and number of subject with mild renal impairment of various methods

GFR/CrCl	Mean ± SD		Mean difference ± SE		Correlation (R^2)		N (%) of subjects with GFR < 90 ml/min 1.73 m^2	
	T (n = 60)	PC (n = 37)	T (n = 60)	PC (n = 37)	T (n = 60)	PC (n = 37)	T (n = 60)	PC (n = 37)
Urine CrCl	105.3±39.3	97.0±15.9					22 (36.7)	14 (37.8)
CrCl-CG[1]	84.7±20.9	83.3±18.0	20.6±5.4*	13.7±3.1**	0.02	0.15**	38 (63.3)	24 (64.9)
CrCl-CG[2]	89.8±19.3	88.7±15.9	15.5±4.9*	8.3±2.2**	0.11*	0.40**	34 (56.7)	23 (62.2)
GFR-MDRD	85.7±18.4	83.3±14.6	19.6±4.6*	13.7±1.9**	0.18*	0.50**	40 (66.7)	26 (70.3)
GFR-Rule	120.3±28.3	117.1±21.9	-15.0±4.7*	-20.1±2.4**	0.20**	0.54**	7 (11.7)	4 (10.8)

CG[1], CrCl-CG without BSA correction; CG[2], CrCl-CG with BSA correction; PC, proper urine collection group (see text)
* $p < 0.05$ correlation between urine CrCl and estimated CrCl/GFR in total study group
** $p < 0.05$ correlation between urine CrCl and estimated CrCl/GFR in subjects with proper urine collection

spectively). The incidence of mild renal impairment was similar in the subjects with proper 24-hour urine collection.

Discussion

Assessment of renal function, even in healthy subjects, is important for proper dosing of medications and for evaluation of potential living kidney donors. Because of the insensitivity of Scr for determination of renal function, it is not uncommon for people to have Scr within the normal range despite having significant renal impairment[16]. Therefore, accurate and precise estimation of GFR is crucial. Unfortunately, this report demonstrated a number of serious limitations of application of commonly used equations in Thai healthy subjects.

The present study showed that both CrCl-CG and GFR-MDRD significantly underestimate 24-hour urine CrCl. Estimated GFR using MDRD equation was lower than CrCl and was understandable because the CrCl is the summation of GFR and tubular creatinine secretion. On the other hand, the value of urine CrCl was expected to be close to CrCl-CG, which was designed to predict 24 hour urine CrCl. These findings contradicted a previous study[12]. The discrepancies could be explained partly by the different race and/or by the limitation of urine collection. However, the data regarding the renal function assessment in healthy subjects with normal Scr adults have almost uniformly concluded that the CG and MDRD equation significantly underestimate standard measured GFR[6-11,13].

Accurate assessment of GFR is important for identifying and stratifying patients at risk of renal disease. The presented data showed that the incidence of low CrCl/GFR (defined as CrCl/GFR value of < 90 ml/min per 1.73 m^2) was highly variable ranging from 10 to 73% (Table 2). According to CG and MDRD equations, incidence of such a group was surprisingly high (57, 67% respectively). A recent study found that the GFR was underestimated by 29% in healthy population

using the MDRD equation[10]. In addition, measured GFR was about 26% higher in healthy persons than in patients with CKD at the same Scr level, age and sex[10]. Therefore, the use of the CG and MDRD equations to predict GFR would overestimate the prevalence of CKD based on the level of estimated GFR. In clinical application, because the CG and MDRD estimates appear to underestimate true GFR, one could accept any individual with normal estimated CrCl/GFR as having normal renal function, if no evidence of renal disease is present. However, this strategy needs to be approved over a period of time.

The presented data demonstrated that prediction equations using either the CG or MDRD performed poorly in subjects of Thai origin (R^2 = 0.1, 0.18 respectively). These findings were consistent with other studies reporting measurement of GFR in healthy adults[6-13]. Although the performance of the equations improved after selecting subjects with proper urine collection, it still remained suboptimal (R^2 = 0.4, 0.5 respectively). This can be partly explained by the fact that MDRD equation was developed from the patients with moderate to severe renal failure and patients without renal disease were excluded from the present study[4]. The CG equation was derived from patients mainly on medical wards and with mean Scr ranging from 0.99-1.78 mg/dl. Therefore, the study group was not healthy and had a relatively high Scr compared to healthy subjects. In contrast the study population comprised healthy adults without any systemic disease and with a mean Scr of 0.95 mg/dl.

The limitations of the present study should be mentioned. First, the use of 24-hour urine collection as the referent method for GFR estimation can be unreliable. This method has many drawbacks, including errors with either both under or over-collection of 24-hour urine and also that produced by tubular secretion of creatinine. Several investigators have recommended abandoning urine CrCl as a means of measuring GFR[17]. Second, the standardization of Scr calibration including that with a Konelab 60 analyzer was not available. Coresh et al[18] demonstrated that the magnitude of the difference in calibration of Scr measurements would result in a large difference in estimated GFR regardless of the equations used to estimate it. The third shortcoming of the present study was the small size of subjects, which, with exclusion of diabetic, hypertensive, obese and elderly subjects that will limit the application of the present results in them.

In conclusion, the performances of the recommended prediction equations were suboptimal for bedside renal function assessment in healthy Thai adults. Further research is required to develop more reliable methods for estimating GFR that could be applicable across different racial groups.

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References

1. Manjunath G, Sarnak MJ, Levey AS. Prediction equations to estimate glomerular filtration rate: an update. Curr Opin Nephrol Hypertens 2001; 10: 785-92.
2. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39: S1-266.
3. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31-41.
4. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999; 130: 461-70.
5. Levey AS, Greene T, Kusek JW, Beck GL, Group MS. A simplified equation to predict glomerular filtration rate from serum creatinine [Abstract]. J Am Soc Nephrol 2000; 11: A0828.
6. Bertolatus JA, Goddard L. Evaluation of renal function in potential living kidney donors. Transplantation 2001; 71: 256-60.
7. Bostom AG, Kronenberg F, Ritz E. Predictive performance of renal function equations for patients with chronic kidney disease and normal serum creatinine levels. J Am Soc Nephrol 2002; 13: 2140-4.
8. Vervoort G, Willems HL, Wetzels JF. Assessment of glomerular filtration rate in healthy subjects and normoalbuminuric diabetic patients: validity of a new (MDRD) prediction equation. Nephrol Dial Transplant 2002; 17: 1909-13.
9. Lin J, Knight EL, Hogan ML, Singh AK. A comparison of prediction equations for estimating glomerular filtration rate in adults without kidney disease. J Am Soc Nephrol 2003; 14: 2573-80.
10. Rule AD, Larson TS, Bergstralh EJ, Slezak JM,

Jacobsen SJ, Cosio FG. Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease. Ann Intern Med 2004; 141: 929-37.
11. Rule AD, Gussak HM, Pond GR, Bergstralh EJ, Stegall MD, Cosio FG, et al. Measured and estimated GFR in healthy potential kidney donors. Am J Kidney Dis 2004; 43: 112-9.
12. Mahajan S, Mukhiya GK, Singh R, Tiwari SC, Kalra V, Bhowmik DM, et al. Assessing glomerular filtration rate in healthy Indian adults: a comparison of various prediction equations. J Nephrol 2005; 18: 257-61.
13. Poggio ED, Wang X, Greene T, Van Lente F, Hall PM. Performance of the modification of diet in renal disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease. J Am Soc Nephrol 2005; 16: 459-66.
14. Mariat C, Alamartine E, Barthelemy JC, De Filippis JP, Thibaudin D, Berthoux P, et al. Assessing renal graft function in clinical trials: can tests predicting glomerular filtration rate substitute for a reference method? Kidney Int 2004; 65: 289-97.
15. DuBois D, DuBois EF. A formula to estimate the approximate surface area if height and weight be know. Arch Intern Med 1916; 17: 863-71.
16. Duncan L, Heathcote J, Djurdjev O, Levin A. Screening for renal disease using serum creatinine: who are we missing? Nephrol Dial Transplant 2001; 16: 1042-6.
17. Walser M. Assessing renal function from creatinine measurements in adults with chronic renal failure. Am J Kidney Dis 1998; 32: 23-31.
18. Coresh J, Astor BC, McQuillan G, Kusek J, Greene T, Van Lente F, et al. Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. Am J Kidney Dis 2002; 39: 920-9.

การประเมินการทำงานของไตเมื่ออยู่ข้างเตียง: การเปรียบเทียบระหว่างสมการต่าง ๆ ที่ใช้คำนวณการทำงานของไตในคนไทยปกติ

เจริญ เกียรติวัชรชัย

วัตถุประสงค์*: เพื่อเปรียบเทียบการใช้สมการต่างๆ ในการคำนวณหาอัตราการกรองผ่านโกลเมอรูลัสและการขจัดครีอะตินีน (GFR และ CrCl ตามลำดับ) ในคนไทยปกติ*

วัสดุและวิธีการ*: คนไทยที่มีอายุระหว่าง 18-60 ปีและมีสุขภาพแข็งแรงจำนวน 60 คนได้รับการตรวจปัสสาวะวัดระดับครีอะตินีนในซีรัมและในปัสสาวะ 24 ชั่วโมง จากนั้นประเมินการทำงานของไต โดยใช้สมการที่เสนอโดย Cockcroft-Gault, MDRD และ Rule โดยเรียกผลลัพธ์ที่คำนวณได้ว่า CrCl-CG, GFR-MDRD และ GFR-R ตามลำดับ จากนั้นนำค่าเหล่านี้มาเปรียบเทียบกับ CrCl ในปัสสาวะ*

ผลการศึกษา*: ค่าเฉลี่ยของ CrCl ในปัสสาวะ เท่ากับ 105.3 $\pm$ 39.3 มิลลิลิตรต่อนาที ต่อ 1.73 ตารางเมตร ซึ่งสูงกว่า CrCl-CG และ GFR-MDRD อย่างมีนัยสำคัญทางสถิติ ส่วนอุบัติการณ์ของภาวะไตเสื่อมแตกต่างกันมาก เมื่ออาศัยเกณฑ์จากการประเมินหน้าที่ไตที่น้อยกว่า 90 มิลลิลิตรต่อนาที ต่อ 1.73 ตารางเมตร และคิดเป็นประมาณร้อยละ 60 จากการประเมินด้วย CrCl-CG และ GFR-MDRD นอกจากนั้นยังพบว่า R^2 ซึ่งแสดงถึงความสัมพันธ์ระหว่างการประเมินการทำงานของไตจากการใช้สมการและ CrCl ปัสสาวะมีค่าต่ำ*

สรุป*: การประเมินการทำงานของไตในคนไทยที่มีสุขภาพแข็งแรงด้วยการใช้สมการ CG และ MDRD มีความคลาดเคลื่อนและต่ำกว่าค่าที่แท้จริง จึงควรมีการศึกษาวิจัยเพื่อสร้างสมการใหม่ที่สามารถนำมาใช้ประเมินการทำงานของไตที่เชื่อถือได้ต่อไป*