Difference Between Estimated Glomerulofiltration Rate by Modification of Diet in Renal Diseases and Cockcroft-Gault Formula in General Population

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Abstract

To characterize the differences between the estimated glomerular filtration rate (eGFR) by using Cockcroft-Gault (CG) and Modification of Diet in Renal Diseases (MDRD) formula. We retrospectively reviewed individuals in a hospital-based health-check program from 2003 to 2006. eGFR was calculated by MDRD formula (MDRD = 186 x $[SCr]^{-1.154}$ x $[age]^{-0.203}$ x [0.742 if female]) or CG ([(140-age) x weight (kg)]/(SCr x 72) x [0.85 if female] and was adjusted for body surface area of 1.73 m^2). A total of 7832 (3264 men and 4559 women) individuals with a mean age of 64±11.4 year-old were studied. Mean eGFR by MDRD and CG formula was 78.6±21.3 and 71.5±21.6 (p<0.0001) respectively. The mean MDRD-CG was 7.1±10.7 revealing that MDRD estimates were higher than CG estimates. The values of MDRD-CG correlated positively with age (r=0.067, p<0.0001) and negatively with body mass index (r= -0.549, p<0.0001) and serum creatinine (r= -0.069, p<0.0001). The MDRD-CG was significantly higher in male, individuals with hypertension, and those with diabetes (p<0.001, p=0.002, and p<0.001). In multiple linear regression analysis, age, gender, BMI, serum creatinine, hypertension and diabetes were independently associated with the differences between MDRD and CG formula. The difference between MDRD and CG formula is associated with age, gender, BMI, serum creatinine, hypertension, and diabetes. In clinical practice, physicians should be aware of these differences. (J Intern Med Taiwan 2009; 20: 148-154)

Key Words：BMI; Estimated glomerular filtration rate; Elderly; Cockcroft-Gault formula; Modification of diet in renal disease formula

Introduction

In general practice, a variety of mathematical formulas are provided for a rapid estimation of renal function which is important for general assessments of renal disease and the adjustments of drug dosages. These formulas contain common variables such as age, body weight, gender, serum creatinine, and albumin blood urea nitrogen levels. In February 2002, the Kidney Disease Outcome Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF) published clinical practice

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guidelines for chronic kidney disease1. This guideline suggested that the Modification of Diet in Renal Disease (MDRD) formula and the Cockcroft-Gault (CG) formula provide useful estimates of the GFR (eGFR) in adult patients. Some studies suggested that the results of CG formula is closer to 125I-iothalamate renal clearance than the results of MDRD formula in individuals with advanced kidney disease[2,3]. However, there are growing doubts about the accuracy of CG formula in individuals with normal renal function[4,5]. Despite the arguments, the CG formula is one of the most commonly used formulas[6].

In clinical practice, we found that the eGFR calculated by CG formula were higher in the young and lower in the elderly than those done by MDRD formula. A previous study has shown that the values of MDRD-CG were positively associated with age and negatively associated with body mass index (BMI) and serum creatinine in the elderly[7]. Because the previous study enrolled patients younger than 60, the association between MDRD and CG formula in those older than 60 is unknown. In addition, hypertension and diabetes are important risk factors of chronic kidney disease (CKD)[2] and the influence of hypertension and diabetes on the differences of MDRD and CG formula is unknown. This study was conducted to characterize the differences between the eGFR calculated by CG and MDRD formula in general population. Factors related to the differences of eGFR between MDRD and CG formula, including hypertension, diabetes, hyperlipidemia, smoking, alcohol consumption, age, body mass index (BMI), and serum creatinine, were also considered in this study.

Methods

We reviewed the records of the participants who had a general health examination in China Medical University Beigang Hospital from 2003 to 2006. eGFR was calculated by MDRD formula (eGFRMDRD = 186 x [SCr]$^{-1.154}$ x [age]$^{-0.203}$ x [0.742 if female]) or eGFRCG = ([(140-age) x weight (kg)]/(SCr x 72) x [0.85 if female] and adjusted for body surface area of 1.73 m^2). Basic data of the participants including age, gender, body height, body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), cholesterol, triglyceride, and fasting blood sugar were measured. Body mass index (BMI) was calculated by taking weight in kilograms, and the square of the height in meters. Hypertension was defined as a history of hypertension (blood pressure >140/90 mmHg) for > 2 years that required the initiation of antihy pertensive therapy by the primary physician[8]. Diabetes mellitus was defined as a fasting blood glucose level of 140 mg/dL, nonfasting blood glucose of 200 mg/dL, or a history of treatment for diabetes[9]. Smoking was defined as a history of smoking for >2 pack-years[10]. Alcohol consumption was defined as people who drink at least 1 drink a day[11].

Statistical analysis

Data are reported as mean ± SD, or percent frequency, as appropriate. Because the Kolmogorov-Smirnov Test revealed the abnormal distribution of eGFR, the statistical analysis was performed with Wilcoxon test. The correlation between the analyzed values was checked with the Spearmann coefficient. Furthermore, Bland-Altman plot was made to compare the values of GFR predicted with the two methods[12]. This approach depicts the mean difference and 95% confidence interval of the difference, represented by the limits of agreement (mean difference ± 1.96 SD of difference). CKD was defined as an eGFR of less than 60 mL/min/1.73 m^2. The relationship between variables (age, gender, creatinine, and BMI) and eGFR of MDRD-CG was analyzed using multiple linear logistic regressions. In the obtained linear regression model, the values of B, t and p were presented. A $p < 0.05$ was considered statistically significant. All calculations were carried out using a standard statistical package (SPSS for Windows, version[12], SPSS Inc, Chicago, USA).

Results

A total of 7823 (3264 men and 4559 women) in our health examination program were reviewed. The clinical characteristics of entire study population were shown in Table 1. As CKD was defined as an eGFR less than 60ml/min/m21, the prevalence of CKD was 17.6% and 30.3% based on MDRD and CG formula. As shown in Figure 1, the eGFRCG was higher than eGFRMDRD in individuals younger than 50, the values of eGFRCG and eGFRMDRD were similar in those between 50 to 60 year-old, and the value of eGFRMDRD was higher than eGFRCG among those older than 60.

The Bland-Altman plot of the comparison of eGFR with MDRD and CG was shown in Figure 2. The mean MDRD-CG was7.1±10.7 ml/min/1.73 m^2 suggesting that MDRD results were higher than those obtained with CG formula. In most subjects (76.6%, 5992/7823), the MDRD was higher than CG. The values of MDRD-CG positively correlated with age (r=0.067, p<0.0001) and negatively both with body mass index (r= -0.549, p<0.0001) and serum creatinine (r= -0.069, p<0.0001). The prevalence of CKD by age was shown in Figure 3. The prevalence of CKD was higher in CG than MDRD in participants older than 60. Based on eGFR of CG formula, a total of 1195 (15.3%) participants had CKD; however, according to eGFR of MDRD formula, these people were not classified as CKD patients. Mean and 95% CI of eGFR with MDRD and CG formula by age were shown in Figure 1. The difference between eGFR of MDRD and eGFR of CG increased with age.

The mean MDRD-CG of participants with

Table 1. Clinical characteristics of all participants

Age (year)	64.0 ±11.4
eGFR (MDRD)	78.6 ±21.3
eGFR (CG)	71.5±22.6
BMI (Kg/M^2)	24.9 ±3.6
SBP (mmHg)	133 ±23
DBP (mmHg)	77 ±12
Chronic kidney disease (MDRD)	1377(17.1%)
Chronic kidney disease (CG)	2475(31.7%)
Comorbidity	
Hypertension	1859(23.8%)
Diabetes	946(12.1%)
Hyperlipidemia	260(3.3%)
Smoking	1024(13.1%)
Alcohol consumption	985(12.6%)
Hemoglobin (gm/dL)	13.8 ±1.5
Platelet (10^3/uL)	209.4 ±59.1
AST (IU/L)	32.5 ±26.9
ALT (IU/L)	31.7 ±41.9
BUN (mg/dL)	17.8 ±6.5
Creatinine (mg/dL)	1.0 ±0.4
Uric acid (mg/dL)	5.9 ±1.5
Albumin (g/dL)	4.0 ±0.3
Globulin (g/dL)	3.3 ±0.5
Cholesterol (mg/dL)	200 ±40
Triglyceride (mg/dL)	123 ±109
Fasting glucose (mg/dL)	111 ±44

Note: Data expression as Mean± SD or number (percent), as appropriate.
Abbreviations: body mass index, BMI; systolic blood pressure, SBP; diastolic blood pressure, DBP; Aspartate Aminotransferase, AST; Alanine Aminotransferase, ALT; blood urea nitrogen, BUN

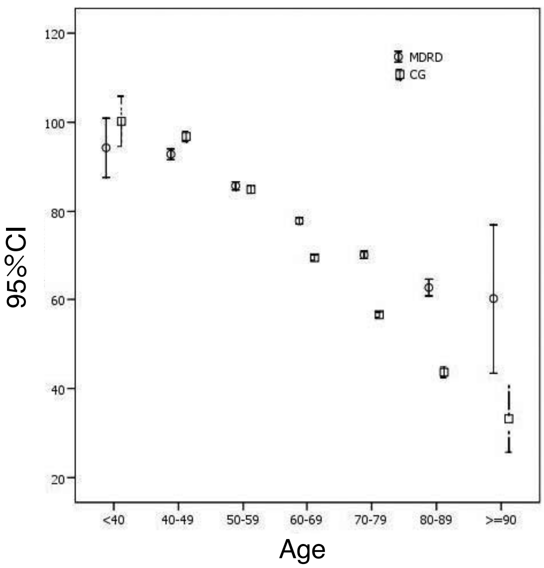

Fig.1.The value and 95% confidence interval of estimated glomerular filtration rate (eGFR) of Cockcroft-Gault (CG) and Modification of Diet in Renal Diseases (MDRD) formula by age.

Table 2. Factors associated with the differences between eGFR by CG and MDRD formula (adjusted R^2=0.814)

	B coefficient	t-test	p value
BMI	-0.500	-100.706	<0.001
Age	0.702	132.595	<0.001
Serum creatinine	-0.317	-58.400	<0.001
Gender	-0.263	-44.401	<0.001
Hypertension	-0.017	-3.414	0.001
Diabetes	0.014	2.812	0.005
Hyperlipidemia	-0.003	-0.555	0.579
Smoking	0.007	1.212	0.225
Alcohol consumption	0.004	0.679	0.497

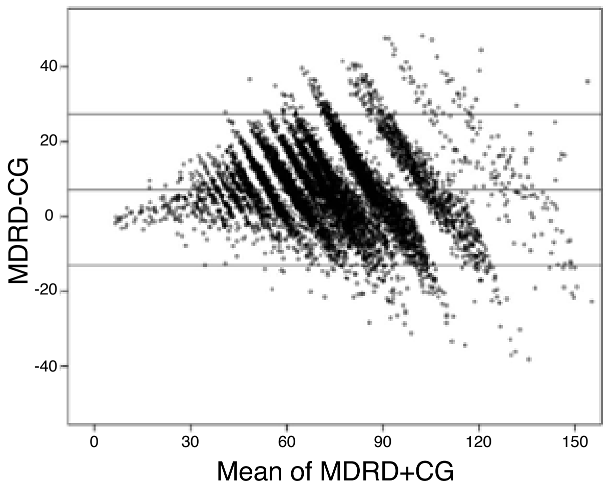

Fig.2.The Bland-Altman plot compared the values of estimated glomerulofiltration rate (eGFR) by Modification of Diet in Renal Diseases (MDRD) and Cockcroft-Gault (CG) formula. It showed the mean difference and 95% confidence interval of the difference, represented by the limits of agreement (mean difference ± 1.96 SD of difference).

The values of MDRD-CG was close to zero suggesting the eGFR of MDRD and CG formula were similar in individuals with mean MDRD+CG less than 30ml/min/m^2. In individuals with mean MDRD+CG more than 30ml/min/m^2, eGFR of MDRD was higher than eGFR of CG by 7ml/min/m^2.

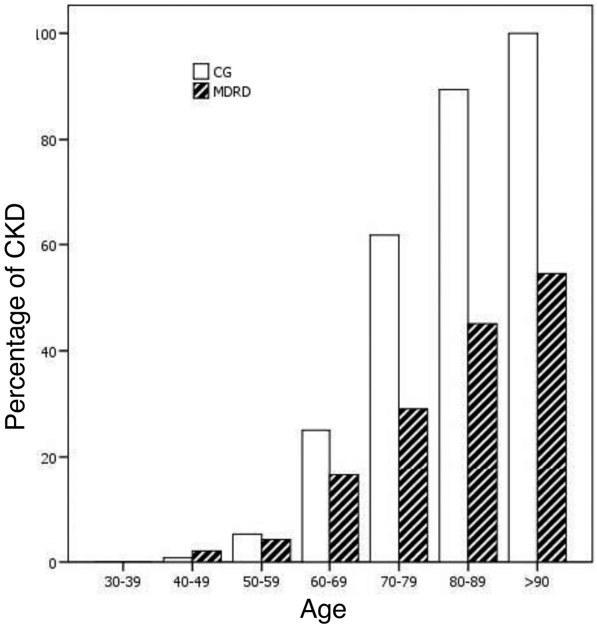

Fig.3.The prevalence of chronic kidney disease (CKD) according to estimated glomerular filtration rate (eGFR) with Cockcroft-Gault (CG) and Modification of Diet in Renal Diseases (MDRD) formula by age.

hypertension was 7.7±9.5, significantly higher than that (6.9±11) of participants without (p=0.004). The mean MDRD-CG of participants with diabetes was 8.5±10.1, significantly higher than that (6.9 ±10.7) of participants without (p<0.001). The mean MDRD-CG in men was significantly higher than that of women (9.5±10.5 vs. 5.4±10.4, p<0.001). The value of R2 of the multiple linear regression analysis was 0.81 indicating that 81% of the variability within the differences between the results of the MDRD and the CG formulas could be explained by the variability in age, gender, BMI, serum creatinine, gender, hypertension, and diabetes. In multiple linear regression analysis, age, BMI, serum creatinine, hypertension, and diabetes were independently associated with the differences between MDRD and CG formula. Among studied parameters, the hyperlipidemia, alcohol consumption, and smoking have no effect on MDRD-CG value (Table 2). The value of MDRD-CG = 18.5+0.719x[age]-0.27x[gender]-0.57x[BMI]-0.32x[Cr]-0.018x[HTN]+0.015x[DM].

Discussion

We have demonstrated that the GFR estimated by MDRD formula were higher than those obtained using the CG equation in individuals older than 60 and the differences increased with age. As shown in the previous study[7], the value of MDRD-CG values is positively correlated with age, and negatively correlated with BMI and serum creatinine. Furthermore, the values of MDRD-CG values were significantly higher in male gender, participants with hypertension, and those with diabetes (Table 2). In addition, the prevalence of CKD estimated by the CG was higher than the one obtained by MDRD, especially in participants older than 60 (Figure 3). The increase of MDRD-CG with age may be explained by the underestimation of CG formula in the elderly[13]. The higher values of MDRD-CG in men may be explained by the underestimate of MDRD in women[14]. A negative correlation between MDRD-CG and BMI was found probably because eGFRMDRD was more likely to be influenced by BMI[2,13,15]. The values of MDRD-CG were higher in patients with hypertension or diabetes because CG formula may underestimate the real GFR in patients with hypertension or diabetes[4].

The Bland-Altman plot is useful to reveal a relationship between the differences and the averages, to look for any systematic bias and to identify possible outliers. If there is a consistent bias, it can be adjusted for by subtracting the mean difference from the new method. If the differences within mean $\pm$ 1.96 SD are not clinically important, the two methods may be used interchangeably[12]. As shown in Figure 2, the value of MDRD-CG was close to zero in those with an eGFR less than 30ml/min/1.73m^2 suggesting that the values of MDRD and CG formula were very close. The mean MDRD-CG increases to 7.1 in those with an eGFR around 30 to 60 ml/min/1.73m^2 suggesting that eGFR calculated by MDRD was higher. Although 7ml/min/1.73m^2 difference may be clinically insignificant, it may result in different classification of CKD stage.

CG formula was introduced by Cockcroft and Gault in 1976 on the basis of observations in predominantly hospitalized male patients[6,16]. The original purpose of this formula was to calculate creatinine clearance. In the Modification of Diet in Renal Disease study, the GFR was measured by 125I-iothalamate renal clearances[17]. From these data, four-variable MDRD equation, used in this study, was derived and became widely used. Because these studies predominantly enrolled non-diabetic patients with moderate CKD, the applicability of the MDRD equation to other populations is unclear, such as individuals without kidney disease, those with more advanced renal dysfunction, the elderly, and individuals of different races. Significant controversy surrounds the issue of eGFR accuracy between MDRD formula and CG formula in patients with end stage renal disease[14,18], the elderly[13], and acute disease[5,16]. The different results of studies may be explained by the different creatinine assay[19,20].

The limitations of our study were single-hospital, cross-sectional, and retrospective design. About 30% of the participants had systemic disease including hypertension, diabetes, and hyperlipidemia. The gold standard measurement for GFR, such as a continuous infusion of 125I-labelled iothalamate and ^{131}I-labelled hippuran for a simultaneous determination of GFR and effective overall plasma flow, was not measured[21,22] in our study. It is difficult to answer the question that which formula is more accurate in predicting GFR. However, the aim of this study is to characterize the clinical differences of eGFR by MDRD and CG formulas. We have shown that the eGFR calculated by MDRD and CG formulas were not different in individuals with GFR less than 30ml/min/m^2. The eGFRCG was higher than eGFRMDRD in individuals younger than 50 and the eGFRCG was lower than eGFRMDRD in those older than 60.

Factors associated with the differences included age, gender, serum creatinine, BMI, diabetes, and hypertension.

In conclusion, our study demonstrates that the differences between the MDRD and CG formula were not only influenced by age, body mass index and serum creatinine but also affected by gender, hypertension, and diabetes. In clinical practice, physicians should be aware of these differences and take them into consideration when they estimate renal functions.

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影響臨床評估腎功能（CG和MDRD公式）的因素

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摘 要

2002年公布的K/DOQI建議在臨床上以Cockcroft-Gault (CG)或Modification of Diet in Renal Diseases (MDRD)公式來評估腎絲球過濾率(estimated glomerular filtration rate, eGFR)作爲慢性腎臟疾病(chronic kidney disease, CKD)分級的依據。但在臨床運用中，我們發現有些患者身上以兩種公式評估腎絲球過濾率存在相當的差異，造成慢性腎臟疾病分級上的困擾。我們回溯研究2003至2006年間，在本院接受成人健檢的7832 (3264位男性和4559位女性)患者，發現以MDRD公式得到的腎絲球過濾率明顯高於以CG公式得到的腎絲球過濾率($p<0.001$)。平均的MDRD-CG可以相差7.1±10.7ml/min/m2，而MDRD-CG的數值與年齡成正相關($p<0.001$)，與肌酐酸的數值和身體質量指數成負相關($p<0.001$ and $p<0.001$)。此外，在男性、高血壓、糖尿病患者，MDRD公式會比CG所得的數值較高，因此，醫師在臨床診斷時應知道這些差異，以利臨床數據的判讀以及診斷上之參考。