Estimating Glomerular Filtration Rate in Asian Patients with Chronic Kidney Diseases from Bioelectrical Impedance Analysis

Bancha Satirapoj MD*, Ouppatham Supasyndh MD**,
Jayanton Patumanond MD, MPH, DSc***, Punbuppa Choovichian MD**

** Division of Nephrology, Department of Medicine, Nopparat Rajathanee Hospital*
*** Division of Nephrology, Department of Medicine, Phramongkutklao Hospital and College of Medicine*
**** Clinical Epidemiology and Medical Statistics Unit, Faculty of Medicine, Chiang Mai University*

Background: *Estimation of glomerular filtration rate (GFR) is usually determined from 24-hour urine collection, but it is time-consuming, and difficult in clinical practice. The authors attempted to select an accurate and safe, but more convenient test to obtain an estimated GFR.*
Objective: *To compare estimation of GFR by Bioelectrical impedance analysis (BIA) with GFR calculated by 24-hour urine averaged creatinine clearance and urea clearance (Ccr-Cu-GFR).*
Material and Method: *The authors examined 79 non-diabetic chronic kidney disease (CKD) patients that had estimated GFR between 15 and 89 ml/min/1.73 m^2. Subjects were categorized into three subgroups according to K/DOQI-CKD classification: GFR of 60-89 ml/min/1.73m^2 (stage 2, 5 subjects), 30-59 ml/min/1.73m^2 (stage 3, 31 subjects), and 15-29 ml/min/1.73m^2 (stage 4, 43 subjects).*
Results: *The mean value of Ccr-Cu-GFR was 33.79 $\pm$ 14.78 ml/min/1.73 m^2 and GFR by BIA (BIA-GFR), 34.63 $\pm$ 14.86 ml/min/1.73 m^2 with no overall statistical differences (p = 0.838). In stage 3 CKD patients, the mean BIA-GFR and Ccr-Cu-GFR were similar (38.84 $\pm$ 12.47 vs 41.16 $\pm$ 9.17, p = 0.399) while in stage 2 CKD, BIA-GFR tended to underestimate (63.50 $\pm$ 19.35 vs 70.94 $\pm$ 7.82, p = 0.407) and in stage 4 CKD, BIA-GFR significantly overestimated Ccr-Cu-GFR (27.31 $\pm$ 9.11 vs 23.76 $\pm$ 5.68, p = 0.040).*
Conclusion: *The findings suggest that BIA-GFR in non-diabetic CKD patients closely resembled with Ccr-Cu-GFR especially in stage 3 CKD patients. BIA-GFR may be considered as a more convenient test for an assessment of GFR in non-diabetic CKD patients.*

Keywords: *Glomerular filtration rate (GFR), Bioelectrical impedance analysis (BIA), Chronic kidney disease (CKD)*

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Glomerular filtration rate (GFR) provides an excellent measure of the kidney filtering capacity. Estimation of GFR is clinically used to assess the level of kidney function and to follow the course of chronic kidney diseases (CKD). An accurate determination of GFR requires measurement of the clearance of inulin or a radiolabeled compound such as iothalamate, DTPA, or EDTA[1-3]. The radioisotopes undergo a small degree of tubular secretion, and overestimate GFR only by a few ml/min in patients with underlying renal insufficiency[2]. Unfortunately, measurement of inulin or iothalamate clearance is not routinely available.

The most widely used measures of GFR in clinical practice are based on 24-hour creatinine clearance[4,5]. Creatinine clearance is more accurate than plasma creatinine in measuring GFR. Approximately 15 percent of urinary creatinine is derived from tubular secretion by the organic cation secretory pathways in the proximal tubule. However, creatinine secretion increases as GFR falls. Among patients with signifi-

Correspondence to : Satirapoj B, Division of Nephrology, Department of Medicine, Nopparat Rajathanee Hospital, Bangkok 10230, Thailand. Phone: 0-2517-4270-1515, E-mail: satirapoj@yahoo.com

cant renal insufficiency, urea clearance significantly underestimates GFR, while that creatinine clearance significantly overestimates. One method to estimate GFR in these patients is to average both creatinine and urea clearances[6]. Although averaging creatinine and urea clearances may be more accurate, it is usually determined from a 24-hour urine collection, since shorter collecting time tends to give less accurate results. The assessment of GFR with averaged creatinine and urea clearance are cumbersome, time-consuming, and difficult in clinical practice. An accurate and safe, but more convenient test to obtain an estimated GFR is needed.

The rate of creatinine production and of subsequent urinary excretion is related to the amount of body muscle mass. Bioelectrical impedance analysis (BIA) has been validated as an accurate, simple and inexpensive method to analyze body muscle mass. A direct measure of body composition by bioelectrical impedance may provide promising direction for improving on the former estimation of GFR using serum creatinine. The authors attempted to compare the values of estimated GFR from plasma creatinine and those from analysis of body cell mass (BCM) by BIA.

Material and Method

This was a cross-sectional analysis of 79 non-diabetic chronic kidney disease (CKD) patients in reference to the K/DOQI-2002 definitions at Phramongkutklao Hospital, Bangkok, Thailand. Subjects were 18 to 90 years of age who were diagnosed with CKD without diabetes. Patients with hypercatabolic states (e.g. sepsis, active infections or acute renal failure), hypervolemic or hypovolemic status which were evaluated by physical examination (e.g. skin turgor, arterial blood pressure, jugular venous pressure) were already excluded. The estimated GFR values ranged between 15 and 90 ml/min/1.73 m^2. The medical chart of each CKD patient was thoroughly reviewed by a nephrologist. The study protocol was approved by the Ethics Committee of Phramongkutklao Hospital and College of Medicine. Written informed consent was requested from all patients.

Measurement of GFR

Averaged of creatinine clearance and urea clearance (Ccr-Cu)

Serum and urinary creatinine were measured by Jaffe's method, while serum and urinary urea were determined by kinetic test with urease method using a standard auto-analyzer. Creatinine clearance (Ccr) and urea clearance (Cu) were calculated on a 24-hour urine collection. GFR was estimated by summing the Ccr and Cu, and divided by two to obtain an average of Ccr and Cu (Ccr-Cu). The clearances were corrected for body surface area of 1.73 m^2. Ccr-Cu measured from two 24-hour urine samples was used as a standard measurement.

GFR prediction equations

The following previously published formulae were used to obtain an estimated GFR:

Modification of Diet in Renal Disease (MDRD) formula[7]:

$= 170 \times \text{serum creatinine}^{-0.999} \times \text{age}^{-0.176} \times (1.180 \text{ if black}) (0.762 \text{ if female}) \times \text{serum urea}^{-0.170} \times \text{albumin}^{+0.318}$

Simplified MDRD formula[8]:

$= 186 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times (1.212 \text{ if black}) (0.742 \text{ if female})$

Cockcroft-Gault formula[9]:

$= [(140\text{-age}) \times \text{weight} (\times 0.85 \text{ if female})]/ 72 \times \text{serum creatinine}$

Plasma albumin concentration was measured by bromcresol-green method using an auto-analyzer. All routine laboratory measurements were performed by standard laboratories with the use of automated methods.

Estimated GFR from BIA

GFR was estimated from plasma creatinine and the value of BCM by monofrequency bioelectrical impedance analysis (BIA 916, Maltron , England) at single frequency: 0.8 MA, 50 KHz.

Predictive equations for GFR based on BCM measured through BIA were derived through multiple linear regression analysis of data obtained from patients. BIA measurements were performed by placing an electrode sensor on the non-access upper arm and both plantar surfaces of feet for several seconds, after the required data (date of birth, sex, race, weight, and height) from each patient were entered.

Statistical method

Data were presented as mean $\pm$ SD or as mean with 95% confidence intervals (95%CI) of deviations. The estimated GFRs from BIA (BIA-GFR), from MDRD formula (MDRD-GFR), from simplified-MDRD formula (s-MDRD-GFR) and from Cockcroft-Gault formula (CG-GFR) were compared with GFR obtained from an average of Ccr and Cu (Ccr-Cu-GFR) by paired *t*-tests. A deviation from Ccr-Cu-GFR of an estimated GFR for each formula and of each patient was calculated. The deviations were plotted against Ccr-Cu-GFR. A regression

line of the deviation as a function of Ccr-Cu-GFR was also drawn to show the trend of the degree and direction of such deviation. Data were categorized into three subsets in reference to CKD stage. The differences between Ccr-Cu-GFR and GFR obtained by each formula and method were calculated and compared by paired *t*-tests. A p-value of less than 0.05 was considered statistically significant.

Results

The clinical characteristics of the subjects are shown (Table 1). Among seventy-nine patients (female 24, male 55, aged 26 to 89 years, mean 59 years), the etiology of CKD was hypertension in 63.3%, chronic glomerulonephritis in 15.2% and interstitial nephritis in 8.9%. Body weight, body mass index (BMI) and serum creatinine levels were 63.27 $\pm$ 12.04 kg and 23.90 $\pm$ 3.84 kg/m^2 and 168.97 $\pm$ 65.02 mol/L respectively.

The deviation of the measured Ccr-Cu-GFR and other estimated GFRs are depicted in Fig. 1-4. For MDRD-GFR, the values generally over-estimated Ccr-Cu-GFR (Table 2). Over-estimation seems to persist throughout the Ccr-Cu-GFR range (Fig. 1). For s-MDRD-GFR and CG-GFR, the trends were similar; an overall over-estimation and throughout the Ccr-Cu-GFR range (Table 2, Fig. 2-3). For BIA-GFR, the overall values were not statistically different from Ccr-Cu-GFR (Table 2), but the direction of deviation significantly changed from an over-estimation in low Ccr-Cu-GFR to an under-estimation in high Ccr-Cu-GFR (Fig. 4).

The K/DOQI guidelines recommend defining a clinical action plan for each patient with CKD on the basis of the stage of disease as defined by the K/DOQI-CKD classification[10]. Therefore, the subjects were categorized into three subgroups: GFR 60-89 ml/min/1.73 m^2 (stage 2; 5 subjects), 30-59 ml/min/1.73 m^2 (stage 3; 32 subjects), and 15-29 ml/min/1.73 m^2 (stage 4; 42 subjects) (Table 3). For subjects with CKD stage 2, the mean CG-GFR, MDRD-GFR and s-MDRD-GFR were slightly more than the mean Ccr-Cu-GFR, but BIA-GFR was less, however all comparisons were non-significant. In stage 3 CKD subjects, the mean CG-GFR, MDRD-GFR and s-MDRD-GFR all showed a statistical over-estimation of the measured Ccr-Cu-GFR, but the mean BIA-GFR was similar to Ccr-Cu-GFR (38.84 $\pm$ 12.47 and 41.16 $\pm$ 9.17, p = 0.399). The mean values of all methods significantly over-estimated the kidney function in stage 4 CKD subjects.

Table 1. Clinical characteristics of the subjects

Characteristics	Total (n = 79)
Age (yr)	59.8$\pm$14.7
Gender (M/F)	55/24
Mean arterial pressure (mmHg) $\pm$ SD	102.47$\pm$11.31
Body weight (kg) $\pm$ SD	63.27$\pm$12.04
Body mass index (kg/m^2) $\pm$ SD	23.90$\pm$3.84
Underlying disease	
- Hypertension (%)	50 (63.3)
- Glomerulonephritis (%)	12 (15.2)
- Interstitial nephritis (%)	7 (8.9)
Smoking (%)	16 (20.3)
Family history of DM (%)	12 (15.2)
Serum creatinine (mol/L)	168.97$\pm$65.02
Serum albumin	4.3$\pm$0.38
Creatinine clearance (ml/min/1.73 m^2)	43.78$\pm$21.65
Urea clearance (ml/min/1.73 m^2)	21.19$\pm$9.82

Discussion

The present study showed that the overall mean BIA-GFR is not significantly different from the mean Ccr-Cu-GFR especially in stage 2 and 3 CKD subjects. By comparison, BIA-GFR seemed to be better than other estimated formulae. Interestingly, the previously published formulae overestimated GFR when compared to the measured Ccr-Cu in our subjects, while BIA-GFR overestimated the measured Ccr-Cu in the lower range and tended to underestimate Ccr-Cu only in the higher range. Serum creatinine and direct measurement of BCM by BIA can be used to simply and accurately predict GFR. One study reported that a prediction of GFR with a high degree of accuracy could be obtained by using a formula containing urinary creatinine, serum creatinine, and muscle mass measured by BIA[11]. In another study, the mean absolute prediction error for creatinine clearance determined by BIA was significantly lower than those obtained from standard GFR predictive equations[12].

Although a higher body mass in general is associated with a greater nephron mass and thus a higher creatinine, body weight is not the best measure of body mass. Weight gain during adult life no longer results in a greater nephron mass[13]. Conversely, substantial muscle atrophy has been shown to occur in patients receiving dialysis compared with healthy controls[14]. In patients who develop kidney diseases, an increase in serum creatinine level caused by GFR reduction may be attenuated by muscle atrophy. The limitations of serum creatinine in predicting renal function are therefore primarily related to muscle mass. The muscle mass index could be used to estimate the

Table 2. Mean and standard deviation of glomerular filtration rate estimated by averaging creatinine and urea clearance (Ccr-Cu), by the other 4 methods and their deviations

Methods	Mean ± SD (n = 79) (ml/min/1.73 m^2)	95%CI of Deviation	p-value
Ccr-Cu	33.79 ± 14.78	-	-
MDRD	41.07 ± 18.64	4.53, 10.03	<0.001
s-MDRD	43.36 ± 17.64	6.76, 12.36	<0.001
CG	40.02 ± 16.62	3.66, 8.80	<0.001
BIA	34.63 ± 14.86	-3.15, 2.56	0.838

Table 3. Mean and standard deviation of glomerular filtration rate estimated by averaging creatinine and urea clearance (Ccr-Cu) and the other 4 methods, classified by CKD stage

Methods	Stage 2 (n = 5)		Stage 3 (n = 32)		Stage 4 (n = 42)	
	Mean ± SD (ml/min/1.73 m^2)	p-value	Mean ± SD (ml/min/1.73 m^2)	p-value	Mean ± SD (ml/min/1.73 m^2)	p-value
Ccr-Cu	70.94 ± 7.82	-	41.16 ± 9.17	-	23.76 ± 5.68	-
MDRD	82.08 ± 28.49	0.376	47.81 ± 14.02	0.011	31.29 ± 9.87	<0.001
s-MDRD	76.04 ± 23.70	0.589	50.30 ± 14.52	0.001	34.16 ± 11.09	<0.001
CG	76.18 ± 26.12	0.633	45.77 ± 11.77	0.056	31.34 ± 9.60	<0.001
BIA	63.50 ± 19.35	0.407	38.84 ± 12.47	0.399	27.31 ± 9.11	0.040

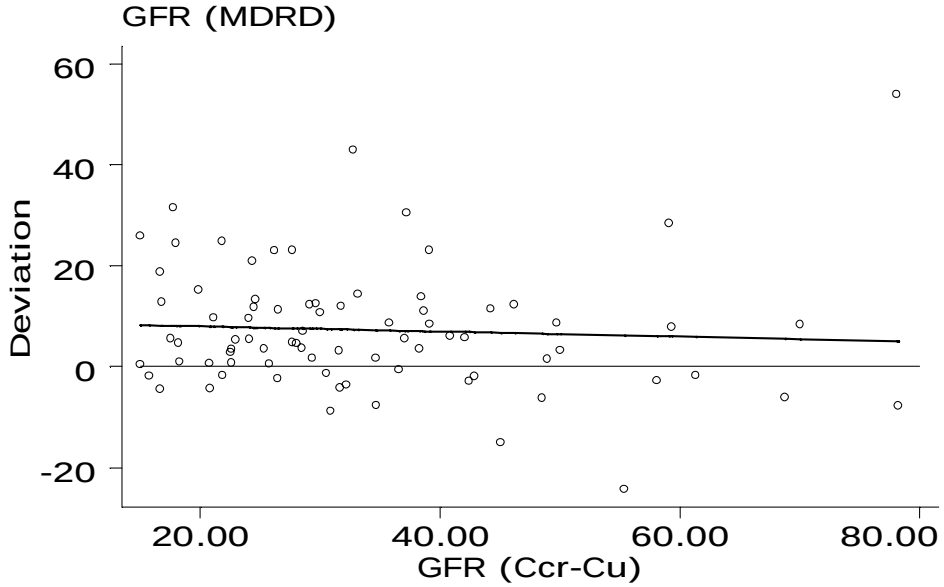

Fig. 1 Glomerular filtration rate estimated from MDRD formula (MDRD) and GFR by averaging creatinine and urea clearance (Ccr-Cu). Zero line represents no deviation or perfect estimation, solid line represents the trend in direction of deviation. All figures are in ml/min/1.73 m^2

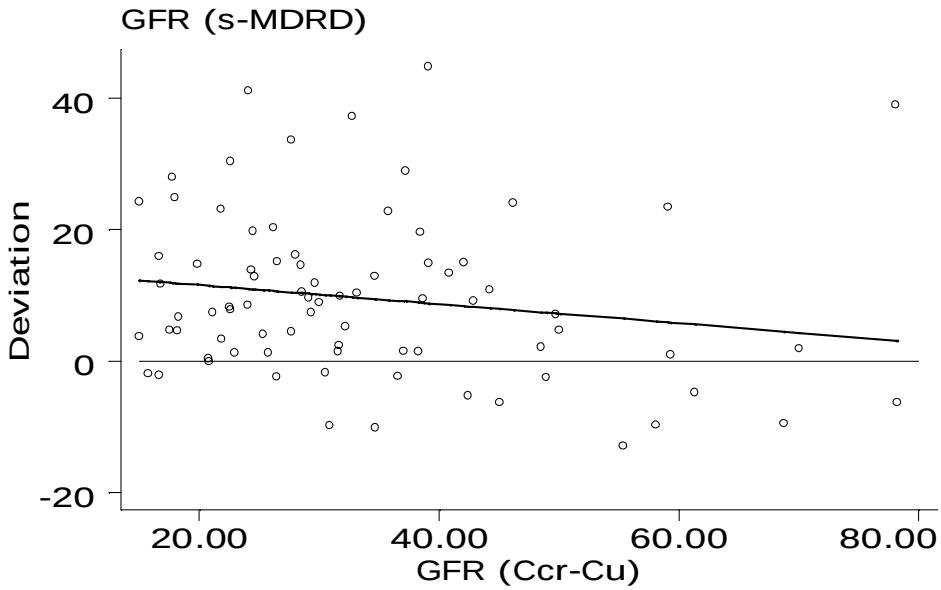

Fig. 2 Glomerular filtration rate estimated from simplified MDRD formula (s-MDRD) and GFR by averaging creatinine and urea clearance (Ccr-Cu). Zero line represents no deviation or perfect estimation, solid line represents the trend in direction of deviation. All figures are in ml/min/1.73 m^2

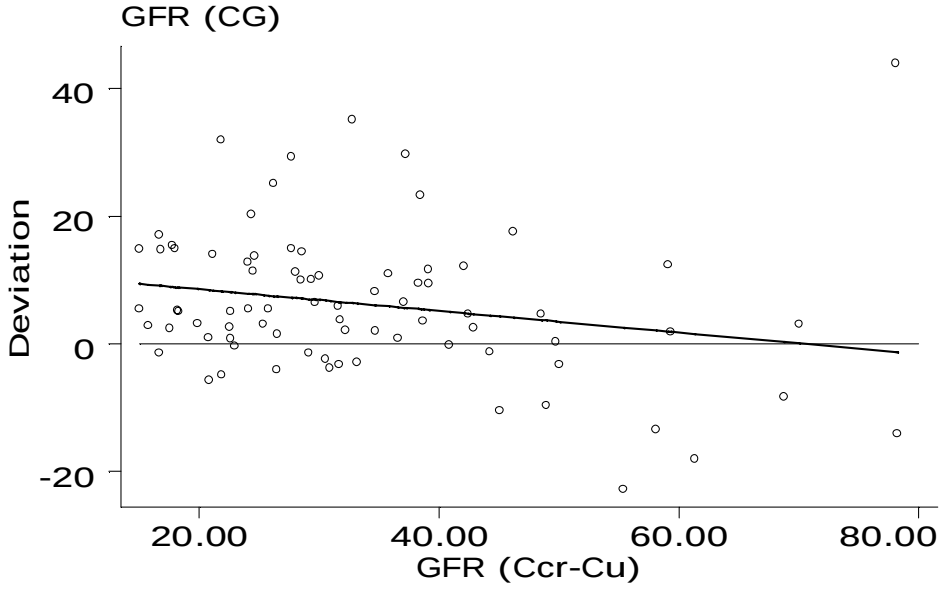

Fig. 3 Glomerular filtration rate estimated from Cockcroft-Gault formula (CG) and GFR by averaging creatinine and urea clearance (Ccr-Cu). Zero line represents no deviation or perfect estimation, solid line represents the trend for direction of deviation. All figures are in ml/min/1.73 m^2

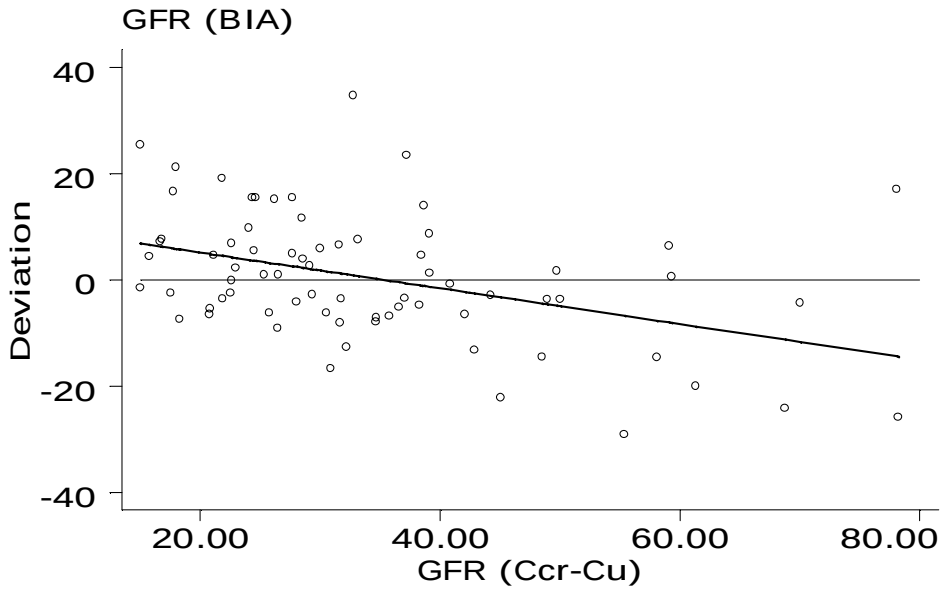

Fig. 4 Glomerular filtration rate estimated from bioelectrical impedance analysis (BIA) and GFR by averaging creatinine and urea clearance (Ccr-Cu). Zero line represents no deviation or perfect estimation, solid line represents the trend in direction of deviation. All figures are in ml/min/1.73 m^2

GFR, BCM, which was determined from BIA, would therefore be the main prediction of GFR.

The accuracy of any clearance technique that relies on urine excretion measurements is compromised by problems associated with obtaining accurate urine collections. Twenty-four hour collections are inconvenient and difficult in clinical practice. The need to collect a urine sample remains a major limitation of the Ccr-Cu technique. BIA was chosen for determining renal function because the machine involved is portable, operator-independent and simple to learn and operate. In addition, accuracy in the measurement of BCM by BIA is independent of such factors as a patient's age, race, gender, hydration status and disease. Furthermore, BIA has proven to be an accurate evaluator of body cell mass while BIA-GFR has been used to estimate the serum creatinine value and BCM. Its use is simple and reflects GFR more accurately than GFR obtaining from the estimating formulae (MDRD, s-MDRD and CG formulae).

The most widely used formula is the one developed by Cockcroft-Gault. However, the formula does not take into account the difference in creatinine production between individuals of the same age and sex or even in the same individual over time. The formula overestimates GFR in individuals who are obese or edematous. The CG formula is, therefore prone to error, especially where a subject's body weight varies from his or her ideal body weight. The prediction of creatinine clearance by this formula had coefficients of variation of the estimate of approximately 23% when compared to isotopically determined GFR[15]. The accuracy in the measurement of BCM by BIA is presumed because of its independency on such mentioned factors because it is based on fat-free mass; therefore it overcomes the bias expected in obese subjects.

The MDRD study had published and elaborated predictive formulae based on iothalamate clearance from a large study subjects with renal diseases[16,17]. Their formulae had a good precision in contrast to the present study, which showed that the average MDRD-GFR was significantly higher than Ccr-Cu-GFR especially in stage 3 and 4 CKD subjects. However, the present results were similar to one study reporting that MDRD-GFR produced estimations of GFR which were systematically higher than those given by the Ccr-Cu method in patients with CKD, this overestimation is particularly marked in some high risk subsets, including elderly patients and those presenting markers of a poor nutritional condition or low lean body mass[17]. The reason for this discrepancy is not

clear, but it may be due to differences in the patient characteristics, as it was known that the MDRD formula may not be accurate in malnutrition patients, and Asian patients generally have lower muscle mass for body weight than whites[18,19]. Because the vast majority of patients included in the present study were Asian, MDRD and CG formulas could therefore, be assessed in a group of subjects whose anthropometric characteristics are only slightly different from those of Americans. The mean weight and BMI in the present study were in fact, lower than those included in the MDRD cohort[7,20].

The present study showed that BIA-GFR was accurate in CKD stage 3. However, the greatest lack of accuracy of BIA-GFR was observed in subjects who had measured GFR of 60-89 ml/min per 1.73 m^2 and 15-29 ml/min per 1.73 m^2. It is probably important to be aware of the range of accuracy for GFR according to the value of estimated GFR.

However, the absence of a comparison with the gold standard for GFR measurement (the renal clearance of inulin or radiopharmaceuticals) could be seen as a pit fall of the study. The authors assumed that the standard GFR used came very close to the inulin clearance, as patients with significant renal insufficiency, Ccr-Cu generally provides an accurate estimation of the true GFR[6]. By the cross-sectional characteristic of the present study, it may not be possible to discuss the differences between the formula to predict renal function changes over time. The number of patients in stage 2 CKD may have been so scarce that it could not detect the difference in the mean GFR for each method.

Conclusion

The findings of the present study suggest that GFR estimated by BIA in non-diabetic CKD are similar to GFR estimated from an averaged Ccr and Cu. GFR estimated from BCM by BIA may be a convenient and cost-effective test for an assessment of GFR in non-diabetic CKD without the burden of 24-hour urine collection.

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การประเมินอัตราการกรองของหน้าที่ไตด้วยวิธี bioelectrical impedance analysis ในผู้ป่วยไทยที่มีโรคไตเรื้อรัง

บัญชา สถิระพจน์, อุปถัมภ์ ศุภสินธุ์, ชยันตร์ธร ปทุมานนท์, พรรณบุปผา ชูวิเชียร

วัตถุประสงค์: เพื่อประเมินอัตราการกรองของหน้าที่ไตด้วย bioelectrical impedance analyzer (BIA) เทียบกับวิธีการตรวจปัสสาวะ 24 ชั่วโมง (ค่าเฉลี่ยของ urea clearance และ creatinine clearance, Ccr-Cu-GFR)

วัสดุและวิธีการ: ศึกษาในผู้ป่วยไตเรื้อรังที่มีค่าอัตราการกรองของหน้าที่ไต (glomerular filtration rate, GFR) อยู่ระหว่าง 15 ถึง 89 มม./นาที/ 1.73 ม^2 จำนวน 79 ราย และแบ่งผู้ป่วยออกเป็น 3 ระยะตาม K/DOQI-CKD classification คือ ระยะที่ 2 GFR เท่ากับ 60-89 มม./นาที/ 1.73 ม^2 จำนวน 5 ราย, ระยะที่ 3 GFR เท่ากับ 30-59 มม./นาที/ 1.73 ม^2 จำนวน 31 ราย และระยะที่ 4 GFR เท่ากับ 15-29 มม./นาที/ 1.73 ม^2 จำนวน 43 ราย

ผลการศึกษา: ค่าเฉลี่ยรวม GFR ในผู้ป่วยไตเรื้อรังทั้ง 2 วิธีไม่มีความแตกต่างกัน (Ccr-Cu-GFR เท่ากับ 33.79 $\pm$ 14.78 มม./นาที/ 1.73 ม^2 และ BIA-GFR เท่ากับ 34.63 $\pm$ 14.86 มม./นาที/ 1.73 ม^2, p = 0.838) และ: ค่าเฉลี่ย GFR แต่ละระยะพบว่า ค่าเฉลี่ย BIA-GFR เทียบกับ Ccr-Cu GFR ในระยะที่ 2 (63.50 $\pm$ 19.35 มม./นาที/ 1.73 ม^{2}เทียบกับ 70.94 $\pm$ 7.82 มม./นาที/ 1.73 ม^2, p = 0.407) และระยะที่ 3 (38.84 $\pm$ 12.47 มม./นาที/ 1.73 ม^2 เทียบกับ 41.16 $\pm$ 9.17 มม./นาที/ 1.73 ม^2, p = 0.399) ไม่มีความแตกต่างกันเช่นกัน ขณะที่ค่าเฉลี่ย BIA-GFR มากกว่า Ccr-Cu GFR ในระยะที่ 4 (27.31 $\pm$ 9.11 มม./นาที/ 1.73 ม^2 เทียบกับ 23.76 $\pm$ 5.68 มม./นาที/ 1.73 ม^2, p = 0.040)

สรุป: การตรวจวัด BIA-GFR มีค่าใกล้เคียงกับวิธีมาตรฐาน Ccr-Cu GFR ในผู้ป่วยไตเรื้อรังดังนั้น BIA-GFR น่าจะเป็นวิธีที่ใช้ในการตรวจวัดอัตราการกรองของหน้าที่ไตที่เหมาะสม