Accuracy of modification of diet for renal disease and Cockcroft-Gault equations as compared to the radioisotope double sample method: A study in patients with acute renal failure

Original Article

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ABSTRACT

Introduction: We intended to assess the accuracy of re-expressed Modification of Diet for Renal Disease (MDRD) and Cockcroft-Gault (CG) equations to estimate glomerular filtration rate (GFR) in chronic kidney disease in two different etiologies of acute renal failure (ARF): acute tubular necrosis (ATN) and acute glomerulonephritis (AGN).

Methods: Patients admitted for ARF or the patients complicated with ARF during the course of their hospitalization were enrolled to the study (n=21; 14 females and 7 males; 11 ATN and 12 AGN). When the plasma creatinine reached a steady state (<15% change in two consecutive days), GFR was measured with double plasma sample method (GFR_{DPSM}) using ^{99m}Tc-DTPA. GFR was also estimated by MDRD (GFR_{MDRD}) and CG (GFR_{CG}) equations.

Results: The patients aged 44.8±19.5 years and weighted 67.8±10.7kg. GFR_{DPSM} (32.9±14.7 ml/min) was statistically different from the GFR_{MDRD} (11.6±8.2 ml/min; $p<0.001$) and CG-GFR (16.5±10ml/min; $p<0.001$). The difference between DPSM-GFR and MDRD-GFR was statistically significant in patients with either ATN (n=11; 31.9±15.0 vs. 11.7±10.3ml/min and p=0.001) or AGN (n=10; 34.1±15.1 vs. 11.4±5.6 ml/min and p=0.001); similarly the GFR_{CG} was lower than GFR_{DPSM} in patients with either ATN (16.5±12.5ml/min and $p<0.01$) or AGN (16.3±7.1ml/min and $p<0.005$). No statistically significant correlation was found between the GFR_{DPSM} and GFR_{MDRD} (r=0.34; p=0.13) but GFR_{DPSM} and GFR_{CG} values were correlated (r=0.48; p=0.03). Out of subjects with GFR_{DPSM} >30, 92.3% had GFR_{MDRD} <30ml/min and 84.6% had GFR_{CG} <30ml/min.

Conclusion: Our results indicate that MDRD and CG equations were substantially inaccurate in patients with ARF. More precise methods of GFR evaluation is recommended in these patients.

Key words: Acute glomerulonephritis; Acute tubular necrosis; Acute renal failure; Cockcroft-Gault equation; Double plasma sample method; Diet

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INTRODUCTION

Accurate determination of glomerular filtration rate (GFR) requires measurement of inulin clearance or application of specific radionuclide techniques [1]. The use of GFR estimates based on various equations including as Cockcroft-Gault (CG) or modification of diet for renal disease (MDRD) formulas are more convenient and advocated by guideline to approximate renal function in chronic kidney diseases (CKD) [2]. These equations are based on serum creatinine level, anthropometrics and demographic data and their application in non-steady state acute renal failure (ARF) is under question.

The MDRD formula has been validated with good accuracy in patients with moderate to advanced kidney disease (GFR<60 ml/min) with certain drawbacks especially in diabetic or obese patients and kidney transplant recipients. Furthermore, its accuracy was not optimal as a screening test among healthy individuals [3]. Some authors also suggest a back-calculating method using this formula to estimate baseline serum creatinine concentration for calculating the serum creatinine changes in patients who present with ARF but without a baseline measurement of serum creatinine [4, 5]. However, the formula is not yet validated for this purpose in a prospective study [6]. Similarly the robustness of CG formula which has been generally used for more than 30 years is not accepted in certain conditions including diabetes and post-renal transplantation [7-9]. The precision of this formula is also questioned in general and in particular conditions including acute tubular necrosis (ATN) where the actual renal function is not essentially compromised [10]. Among the hospitalized patients ARF is common (5%) where the monitoring of renal function may be crucial to decide whether or not hemodialysis is required [11]. While the GFR decreases in ARF, creatinine excretion becomes greater than the filtration causing overestimation of the GFR by creatinine clearance estimations [12]. According the MDRD formula which was originally designed to estimate GFR instead creatinine clearance may be more appropriate in ARF than CG equation. In this context, also considering the effect of ethnicity and differences in body musculature, we intended to assess the accuracy of GFR estimates by CG and MDRD equations in patients with ARF comparing with a more accurate nuclear medicine procedure, double plasma sample method (DPSM).

METHODS

Patients

The study was conducted between March 2008 and March 2009 in a referral university hospital. The study protocol was approved by the ethics committee of Tehran University of Medical Sciences and written informed consents were obtained from all participants.. The participants were recruited from those admitted with the diagnosis of acute renal failure (ARF) or those hospitalized for other medical conditions complicated with ARF. ARF was defined as an acute and sustained increase in serum creatinine concentration of 44.2 µmol/L if the baseline was less than 221 µmol/L, or an increase in serum creatinine concentration of more than 20% if the baseline was more than 221 µmol/L [13]. Patients with suspected post-renal causes were not included. The participants comprised two major categories: subjects with ischemic or nephrotoxic (i.e. due to acute hemorrhage, volume depletion or medications) acute tubular necrosis (ATN); and subjects with acute glomerulonephritis (AGN) including post-infectious, antibody or cell mediated AGN proved by biopsy.

Measurements

The patients were followed for stabilization of plasma creatinine level indicated by less than 15% variation in plasma creatinine measurements in two consecutive days. They were then referred for the measurement of GFR with ^{99m}Tc-diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA) using double plasma sample method (DPSM).

On the examination day, patients were instructed to take 300-500 ml water after breakfast. Following admission to nuclear medicine department, a bolus dose of 300-500 µCi ^{99m}Tc-DTPA was injected into an anti-cubital vein. Radioactivity of the syringe was measured before and after injection to calculate the injected dose. Afterward, blood samples were collected by 2 and 4 hours of injection and plasma activity was counted using a Gamma Counter (Kontron, Swiss) set for 20% energy window around 140 kev (126-154 kev). Finally plasma clearance of ^{99m}Tc-DTPA was calculated (Table 1) [14]. Plasma Cr levels were also recorded at the same time to estimate GFR using CG and MDRD equations (Table 1).

Statistical analysis

SPSS software (SPSS, Chicago, IL, USA; Version 15 for Windows Evaluation) was employed. Data was explored for the skewness by Kolmogorov-Smirnov test. Data transformation was considered where appropriate. The continuous variables were compared in different groups using independent sample t-tests. Correlation between GFR_{CG} or GFR_{MDRD} with GFR_{DPSM} was assessed by curve estimation analyses and the data of statistically significant models (i.e. simple linear and exponential regression) are reported.

Table1. The equations for calculation of glomerular filtration rate (GFR) by double plasma sample method (GFR_{DPSM}), Cockcroft-Gault formula (GFR_{CG}) and modification of diet for renal disease equation (GFRMDRD).

Glomerular filtration rate	Equation
Double plasma sample method	$GFR_{DPSM}=\{D*Ln\ (P_1/P_2)*Exp\ [(t_1*LnP_2-t_2*LnP_1)/\ (t_2-t_1)]\}/(t_2-t_1)$ D is injected dose (count/min/ml); P_1 is plasma count at 2nd hour (count/min/ml); P2 is plasma count at 4th hour (count/min/ml); t_1 is 120 min; and t_2 is 240 min
Cockcroft-Gault	GFR_{CG}=(140 − age × weight) / (72 × serum creatinine) × (0.85, if patient is female).
Modification of diet for renal disease	GFR_{MDRD} =175 × (serum creatinine)$^{-1.154}$ × (Age)$^{-0.203}$× (0.742, if patient is female)

Dimensions of serum creatinine, weight and age in these formulas are mg/dl, kilograms and years, correspondingly.

Between- and within-subjects analyses of variances were conducted to explore the effect of underlying cause of ARF (i.e. ATN or AGN) on the difference between the GFR_{DPSM} with GFR_{CG}/GFR_{MDRD}. Contingency tables were generated for calculation of the accuracy of the CG and MDRD equations to classify subjects with DPSM based GFR>30 (grade ≤3 renal failure). P values below 0.05 were considered statistically significant.

RESULTS

The study included 21 patients, 7 male and 14 female patients, aged 44.8±19.5 yrs and weighted 67.8±10.7 kg with serum creatinine level of 6.9±3.9 mg/dl. No statistically significant difference was noted between patients with ATN and AGN in terms of the age (49.4±22.2 vs. 39.7±15.5 years, p=0.341), weight (71±12.5vs. 64.2±7.4kg, p=0.169) and plasma creatinine levels (7.8±4.7 vs. 5.9±2.5 mg/dl, p=0.459). The values of estimated GFR_{MDRD} and GFR_{CG} were skewed (Kolmogorov-Smirnov P<0.01 for both). The estimations of GFR by CG or MDRD equations were significantly different from that of DPSM, in all patients as well as in subgroups of subjects with ATN or AGN (Table 1). The GFR_{CG}, GFR_{MDRD} and GFR_{DPSM} were not different between subjects with ATN or AGN (Table 2).

GFR_{CG}, but not GFR_{MDRD} correlated with GFR_{DPSM} adjusted for the etiology of ARF, i.e. ATN and AGN (r= 0.46; p=0.043). This correlation was also statistically significant without adjustment for the cause of ARF (ATN or AGN; r= 0.45; p=0.039; Figure 1). The curve estimation analyses revealed that in addition to simple linear correlation, there is an exponential association between the GFR_{CG} and GFR_{DPSM} (Figure 1). The linear correction equation was GFR_{DPSM}= 22+0.67* GFR_{CG}. The standardized residual of regression for GFR_{CG} on GFR_{DPSM} increased with the GFR_{DPSM} values (Figure 2). General linear model (with adjustment for age and sex) revealed that the correlation of GFR_{CG} and GFR_{DPSM} is the same between the subjects with ATN and AGN (p=0.33).

Table 2. Comparison of the estimates of re-expressed Modification of Diet for Renal Disease (MDRD) and Cockcroft-Gault (CG) equation with the results of double plasma sample method (DPSM) in all participants and separately in subjects with acute tubular necrosis (ATN) or acute glomerulonephritis (AGN).

	CG	MDRD	DPSM
All participants	†16.4(10.0)	†11.6(8.2)	32.9(14.7)
ATN (n=11)	†16.6(12.5)	†11.7(10.3)	31.9(15.0)
AGN (n=12)	†16.3(7.1)	†11.4(5.6)	34.1(15.1)

Data are mean and standard deviation in parentheses. † indicates statistically significant (p<0.05) difference with the values of DPSM.

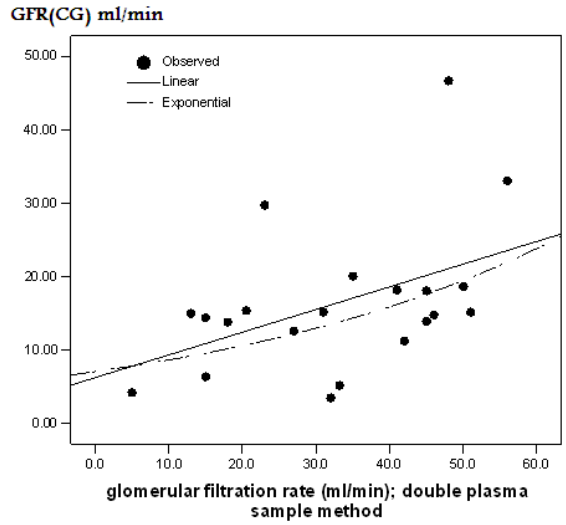

Fig 1. The correlation of the glomerular filtration rate (GFR) by double plasma sample method (GFR_{DPSM}) and Cockcroft-Gault formula (GFR_{CG}).

The MDRD equation misclassified 12 out of 13 subjects (92.3%) with GFR_{DPSM}>30 ml/min (stage 3 renal failure or less) as GFR<30 ml/min (Stages 4 and 5). False positive for stage 4 or 5 renal failure) was 84.6% for CG equation.

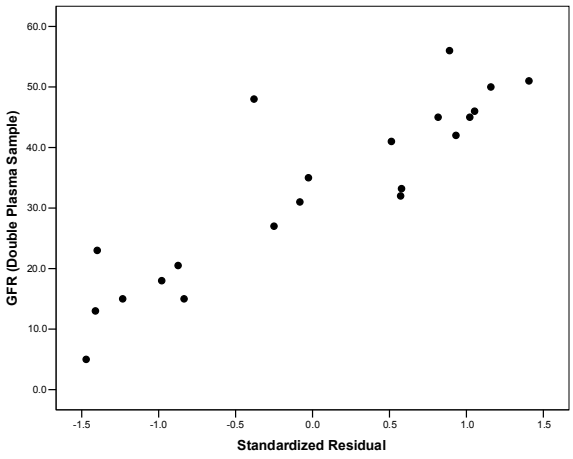

Fig 2. The residual of the regression of glomerular filtration rate (GFR) by double plasma sample method (GFR_{DPSM}) on the GFR by Cockcroft-Gault formula (GFR_{CG}) increases with the GFR level indicating greater imprecision of $GFR_{(CG)}$ for higher GFR values.

DISCUSSION

This study provides several insights. First, the MDRD equation was substantially inaccurate in our subjects with ARF the GFR_{MDRD} values did not correlate with the DPSM based GFR. Also the DPSM based GFR and GFR_{MDRD} values were different. Second, there was a statistically significant difference between the GFR_{CG} and GFR_{DPSM} methods Nevertheless, GFR_{CG} correlated with GFR_{DPSM}. The difference between $GFR_{CG\ and}$ GFR_{DPSM} was more pronounced and uncorrectable for higher GFR values. This underscores the flail of common clinical application of the CG as well as the more up-to-date MDRD formula particularly for less compromised renal functions. Third, the inaccuracies of both equations were obsererved in ARF with different etiologies (i.e. ATN or AGN).

ARF is clinically diagnosed based on abrupt increase in the plasma creatinine and blood urea nitrogen levels [15]. Many patients with ARF are not at high risk for advanced uremia and need for hemodialysis; the extent of the uremia may be disproportionate to the degree of permanent or even temporal renal function impairment. The MDRD formulas for GFR estimation were designed originally based on the data of populations with CKD. In regard to GFR_{CG}, while the overall imprecision of formula based estimation of GFR is essentially accepted [16], the application of the CG formula in chronic kidney disease is widely approved [17, 18]. Many clinicians in our current practice extrapolate the use of the equation based GFR estimations in patients with CKD in ARF situations [19]. We documented the MDRD equation was substantially inaccurate in the population with ARF, with equal inaccuracy in both ATN and AGN subgroups. The MDRD-based GFR estimates were significantly different from and even not correlated with the GFR_{DPSM} values. These findings are in contrast with the report of Hai-xia that MDRD is an accurate method to estimate GFR in levels between 60–89 ml/min compared to other equations [20]. Furthermore, even though a weak correlation was observed between the GFR_{CG} and GFR_{DPSM}, there is still a statistically significant difference between these values. The differences are more remarkable at higher GFR levels. This may lead to underestimation of GFR in acute renal failure especially when renal function is less compromised. Our findings regarding CG formula are in agreement with the study by Nielsen et al indicating that the CG formula underestimates the GFR with a greater propensity for higher values [21-23]. Such underestimation is markedly evident in patient experiencing weight loss [24]. In contrast, it is reported that the CG formula overestimates the actual GFR values mainly in low GFR levels [25, 26]. The overestimation of the GFR by CG is supported theoretically by the fact that formula was calculated based on the data of subjects with normal renal function [27]. Accordingly we documented a significant drawback of the current common clinical application of the formula-based estimation of GFR in ARF. We underscore the more sophisticated method, inulin clearance, is the gold

standard for calculation of GFR; this is a limitation of our study; nevertheless inulin clearance is not appropriate for routine clinical settings.

In hospitalized patients, in addition to renal function, many other factors including fever, immobilization, trauma, hepatic disease and muscle mass may influence the serum creatinine levels by changing its production rate. Furthermore, tubular re-absorption (back-leak) of the creatinine may occur in the situation of low urine flow rate in conditions such as ATN. Increased volume of distribution for creatinine may also occorin very ill patients resulting in rapid changes of serum creatinine levels. The above-mentioned changes may be the essential factor for the inaccuracy of formula-based GFR estimation methods in many hospitalized patients with ARF. Thus the alterations in serum creatinine during ARF may not directly correlate with the real changes in GFR particularly in the first days after the onset of disease. This problem may lead to misjudgement regarding the degree of renal dysfunction in patients with ARF. In fact, the serum creatinine might rise slowly on the first days while the actual disturbed GFR does not show remarkable change over time. Thus, even though the GFR is constant, the patient would progress from low grade to high grade failure over time based on the serum creatinine levels [28].

CONCLUSION

Some Clinicians in common practice entrust on the equation based GFR estimations in ARF with some evidences inferring that the predicted-clearance method correlates acceptably with more sophisticated plasma-clearance method. Our finding highlights the flail of such approach and the need to employ more sophisticated namely DPSM methods.

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