Evaluation of Glomerular Filtration Rate Estimating Formulas in Diabetic Patients with Chronic Kidney Disease

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Abstract

Objective: Measurement of glomerular filtration rate (GFR) is the best determinant in assessment of kidney function for diagnostic and therapeutic purposes. As extremely accurate methods of GFR measurement (i.e. Inulin clearance) are expensive and Time-consuming and due to limitations of the 24 hour urine collection method, some formula have been developed for the GFR measurement. Here we have compared the GFR calculated via CG or MDRD formulas and that measured by creatinine clearance in 24-hour urine collection method in diabetes patients with chronic kidney disease (CKD).

Materials and Methods: This study was performed on 75 diabetes patients with stage 3 or 4 CKD (15-19 ml/min/1.73m^2) in the nephrology clinics of the Yazd medical university. The GFR was measured via CG and MDRD formula and also via creatinine clearance in 24-hour urine collection method. Correlation test and Bland altman plot was utilized to check for the relationship between creatinine clearance and the GFR.

Results: Results show a significant correlation of the GFR calculated via creatinine clearance in 24-hour urine collection with GFR calculated via CG (r= 0.75) and with MDRD (r=0.70) formulas. This correlation was even increased when serum levels of creatinine was >1.5 mg/dL or in patients with stage 4 CKD. Comparison of the differences between GFR calculated via CG or MDRD formulas and creatinine clearance in 24-hour urine collection method using Bland altman showed a lower bias (CG: 17.76; MDRD: 10.64 ml/min/1.73 m^2) and narrower limits of agreement (MDRD: -11.33 – 32.62, CG: -4.68 – 40.20) to the creatinine clearance in 24-hour urine collection for the MDRD formula compared to that for the CG formula.

Conclusion: CG and MDRD correlate well with creatinine clearance in 24-hour urine collection, while MDRD is more accurate in diabetes patients with stage 3 or 4 CKD.

Keywords: Chronic kidney disease, Glomerular filtration, Cockcroft and Gault formula (CG), MDRD

Introduction

Chronic kidney disease (CKD) is a multitude of several pathologic phenomena in relation with kidney abnormal function and a progressive decline in Glomerular Filtration Rate (GFR) (1,2). Increased incidence rate of CKD has threaten world health (3) and brings over financial pressure on health care systems and has

several social psychological consequences(4). The main cause of CKD is diabetes and hypertension. Clinical manifestations of CKD isuremia, which apears very late and quietly (1,4,5). With early detection and treatment of CKD, it is possible to prevent kidney failure and its potential effects on cardiovascular diseases and decrease mortality or at least post-pone it (3,4,6). GFR is the best determinant of kidney function (7-11). At present, National Kidney foundation has advised GFR as a useful tool in defining, screening, staging and evaluation of chronic kidney disease progression (7,8). CKD is classified as stage 1 to 5 based on GFR, regardless of underlying cause (table 1) (5,12). Indications of GFR measurement in CKD are: 1) Early detection of impaired renal function in patients with risk factors, 2) Evaluation of disease progression and prognosis, 3) treatment, and 4) determining ofdialysis and kidney transplantation indication. Although accurate measurement of GFR based on exogenous substances clearance is possible, as it is too complicated, alternative approaches including serum levels of endogenous substances , such as creatinine, has been suggested (8,13). Inulin clearance has been introduced as the golde standard of GFR measurement, but this approach is expensive and time-waisting (4,8,11,14).This method requirements are frequent injection, bladder catheterization, and repeated blood sampling which are difficult (8). GFR can also be measured by creatinine clearance in 24-hour urine collection. In this method, creatinine concentration in serum ,urine and 24-hours urine collection is required (3,14). Twenty four hours urine collection is a limitation of this method, Particularly in non-hospitalized patients (3) (4,7,9). Collection of urine is a main source of errors in this method, so this is not always reliable (10,14). On the other hand, because of glomerular filtration of creatinine and its tubular secretion, GFR calculated here is greater that its real rate (9,10). To overcome this problem, some formula has been developed to calculate creatinine clearance simply, fast and reliable. In this new approach, urine collection is not required and the formulas have been developed based on serum concentrations of creatinine, weight, age and gender (2,4,9,15,16). Two major formula, Cockcroft and Gault (CG, in ml/min) and the Modification of diet in renal disease (MDRD, in ml/min/1.73m^2) are utilized to measure GFR in adults (16,17). However, there are concerns about whether the values obtained from the CG and MDRD formulas are comparable with the measured creatinine clearance of test the aim of our study was to find which formula is a more accurate alternative ofthe 24-hour urine collection method in stage 3 and 4 kidney disease.

Table 1. Classification of chronic kidney disease (CKD)

Stage	Description	GFR ml/min/1/73 m^2
1	Kidney damage with normal or ↑ GFR	≥ 90
2	Kidney damage with mild ↓ GFR	60 – 89
3	Moderate ↓ GFR	30 – 59
4	Severe ↓ GFR	15 – 29
5	Kidney failure	< 15

Materials and Methods

This is a descriptive research which creatinine clearance rate is compared to the GFR measured via CG and MDRD formula. The study samples are CKD patients who came to nephrology clinics of the Shahid Sadouqi University of Medical Sciences, Yazd -2013. Inclusion criteria were: Patients between 35-75 years of old with CDK stage 3 or 4 (GFR: 15-59 ml/min/1.73m^2). The goals of the study explained to the patients and consent was received. Patients were interviewed and a checklist of their general condition was completed. Patient's weight was measured by TRILON scale with an accuracy of 100gr with minimum wearing and without shoes. Height was measured by Seca tool with an accuracy of 0.5 cm. To measure the levels of serum creatinine, 3cc blood sample was taken. To determine the volume of 24-hour urine and its creatinine content, patients were educated how to collect 24 hour urine, by an educational

pamphlet, so they were asked to throw away their first morning urine and collect the rest for 24 hours. Colorimetric method was used to measure creatinine content of the blood samples and urine collection using biosystem diagnostic kits and auto-analyzer system (Prestige- SPA plus- Japan). Then GFR was measured in 3 ways: 1) creatinine clearance in 24-hour urine collection, 2) Cockcroft and Gault (CG) formula and 3) Modification of diet in renal disease (MDRD) formula.

1. Creatinine clearance (ml/min) = U ×V× 1.73 / P ×1440

Where U is urinary creatinine (mg/dl), V is urinary volume in 24 hours (ml), P is serum creatinine (mg/dl)

2. Cockcroft- Gault estimated creatinine clearance (ml/min) = (140-age) ×(weight in Kg) / serum creatinine (mg/dl) × 72 × (0.85 if female).

3. MDRD estimated creatinine clearance (ml/min/1.73m^2) = 186 × [serum creatinine (mg/dl)] -1.154 × (age in years) -0.203 × (0.742 if female).

The results are presented as meam±standard deviation and frequency (%) for quantitative and qualitative variables, respectively. To assess the relationship between creatinine clearance and calculated GFR via CG and MDRD formulas, Pearson correlation coefficient test and Bland altman plot were utilized. To determine the bias, the average of the differences between the creatinine clearance in 24-hour urine collection and the GFR calculated via CG and MDRD formulas, was calculated and separately for each formula. In this study, *P*-values less than 0.01 were considered statistically significant and data analysis was performed using SPSS (ver.18).

Results

Seventy five patients with stage 3 or 4 CKD participated in this sectional research of which 55 (73.3%) were male and 20 (26.7%) were female. Participants were 37-75 years old with an average of 61.1 years. 53 patients (70.7%) were on stage 3 and 22 (29.3%) were on stage 4 of the CKD. Other data are shown in table 2. The mean and the standard deviation of the creatinine clearance in 24-hour urine collection and that of GFR calculated via CG or MDRD formula were compared. Data are shown in table 3. Results show great correlation between creatinine clearance in 24-hour urine collection and the calculated GFR via CG (r=0.75) or MDRD (r=0.70). This correlation was even increased when serum levels of creatinine was >1.5mg/dL and in stage 4 CKD. If creatinine clearance in 24-hour urine collection is adjusted for body surface (m^2), its correlation with MDRD formula shows a slight increase (*P*= 0.00, r=0.73) and a decrease with that of CG (*P*=0.00, r=0.71). Comparison of the differences between creatinine clearance in 24-hour urine collection and the GFR calculated via CG or MDRD using Bland altman plot is shown in figure 1 and 2. These data show that MDRD formula has less bias (CG:17.76 ml/min; MDRD: 10.64ml/min/1.73m^2) to creatinine clearance in 24-hour urine collection and also Narrowerlimits of agreement (CG: -4.68-40.20; MDRD: -11.33-32.62) compared to CG formuls.

Table 2. Demographic characteristics of patients with chronic kidney disease referred to nephrology clinics of Yazd University of Medical Sciences, 2013

Variables	Number (Percentage)
Gender	
Male	55 (73.3%)
Female	20 (26.7%)
Age(years)	61.1 ± 8.44
BMI(kg/m^2)	28.6 ± 4.35
Stage of CKD	
Stage 3	53 (70.7%)
Steage 4	22 (29.3%)
Serum creatinine	
Less than 1.5 mg/dl	28 (37.3%)
More than 1.5 mg/dl	47 (62.7%)
Underlying disease	
Diabetes	75 (100%)
Hypertension	60 (82.6%)
Hyperlipidemia	59 (78.6%)
Heart disease	8 (10.6%)
GI Diseases	4 (5.3%)

Discussion

Frequent assessment of the kidney is an important aspect of management and treatment of several metabolic diseases (4); specifically in the case of renal diseases in which progression can be arrested or delayed if early detection is achieved and appropriate management approach is decided (14). Simple and accurate measurement of the GFR is required to assess the function of the kidney (13). The most common method for GFR measurement is creatinine clearance in 24-hour urine collection (9). Urine collection for 24 hours is not often favorable for patients and this step can be a major source of errors in GFR estimation. Thereby several formulas have been developed to measure GFR based on serum levels of creatinine, so urine collection is not required. The CG and MDRD formula are the most common ones in use (13). Advantages of these formulas are: simple equations, ease of GFR calculation and inexpensiveness (4). Here we have investigated the correlation of the creatinine clearance in 24-hour collection and the GFR calculated via CG and MDRD formula in 75 patients with stage 3 or 4 CKD. Results show great correlation of creatinine clearance in 24-hour collection with the GFR calculated via CG and MDRD formula. This correlation was better when serum levels of creatinine was >1.5mg/dL and in stage 4 CKD. Zubairi et al showed high correlation between creatinine clearance in 24-hours urine collection and the GFR calculated via CG (r=0.77) and MDRD (r=0.78) formula and this correlation was higher in patients whose level of serum creatinine was >1.5mg/dL (CG; r=0.62 and MDRD; r=0.72) rather than patient with serum creatinine <1.5mg/dl (CG; r=0.60 and MDRD; r=0.59) (4). Here we report that according to comparison of the differences between creatinine clearance in 24-hour urine collection and the GFR calculated via CG or MDRD using Bland altman plot, both formula show positive bias and over estimate GFR. Zubairi et al also reported positive bias (MDRD=15.22 and CG=16.30) for GFR calculated via CG or MDRD (4). It is possible that the positive bias and over stimation of GFR observed in this study has been due to errors in urine collection method (13). It may also be due to patients conditions such as differences in ethnicity, BMI, height, weight and diet compared to studies that have approved CG and MDRD validation in GFR calculation (4).

In this study we also demonstrate that the MDRD is more accurate than CG formula in GFR estimation and CG formula estimates glomerular filtration rate slightly higher than the MDRD formula. Rodrigo et al. reported the least bias and the Narrowest limits of agreement between creatinine clearance and GFR calculated by MDRD(18). Al Wakeel et al. compared the rate of inulin clearance with the GFR calculated by CG and MDRD formulas which demonstrated the MDRD has less bias (MDRD= 0.3 and CG=-5.5) and Narrower limits of agreement (MDRD= -14.2-14.8 and CG= -25.6-14.7) than CG (19).

Table 3. Comparison between Creatinine clearance calculated by CG and MDRD equation and 24-hour urine collection

Variable	The overall results		Serum Creatinine <1.5mg/dl		Serum Creatinine >1.5mg/dl		Stage 3		Stage 4	
	mean±SD	Correlation coefficient	mean±SD	Correlation coefficient	mean±SD	Correlation coefficient	mean±SD	correlation coefficient	mean±SD	Correlation coefficient
Creatinine clearance (ml/min)	27.88 ±15.08	r=1	37.77 ±15	r=1	21.98 ±11.78	r=1	32.99 ±14.79	r=1	15.56 ±5.91	r=1
Creatinine clearance (ml/min/1.73m^2)	25.91 ±13.03	r=0.97 *P*=0.000	35.34 ±12.47	r=0.96 *P*=0.000	20.28 ±9.76	r=0.97 *P*=0.000	30.62 ±12.36	r=0.97 *P*=0.000	14.54 ±5.30	r=0.98 *P*=0.000
GFR (CG)	45.64 ±17.19	r=0.75 *P*=0.000	60.46 ±12.69	r=0.50 *P*=0.000	36.81 ±12.94	r=0.76 *P*=0.000	52.92 ±14.31	r=0.62 *P*=0.000	28.08 ±8.79	r=0.79 *P*=0.000
GFR (MDRD)	38.52 ±13.86	r=0.70 *P*=0.000	52.94 ±5.97	r=0.31 *P*=0.000	29.22 ±9.27	r=0.74 *P*=0.000	45.61 ±9.52	r=0.53 *P*=0.000	21.44 ±4.44	r=0.79 *P*=0.000

Rigalleau et al, also demonstrated that the MDRD formula is more accurate than CG in GFR estimation in nephropathy diabetes patients (20). CG formula is weigh-dependent. On the other hand, a significant percent of the patients participating in this study had over-weight and most patients with chronic kidney disease have fluid retention and weight gain associated with it. Over-weight in CKD patients is often due to liquid retention. The major limitation of this study was the lack of GFR comparision with its golden standard, inulin clearance.

Finally, our findings show although the GFR

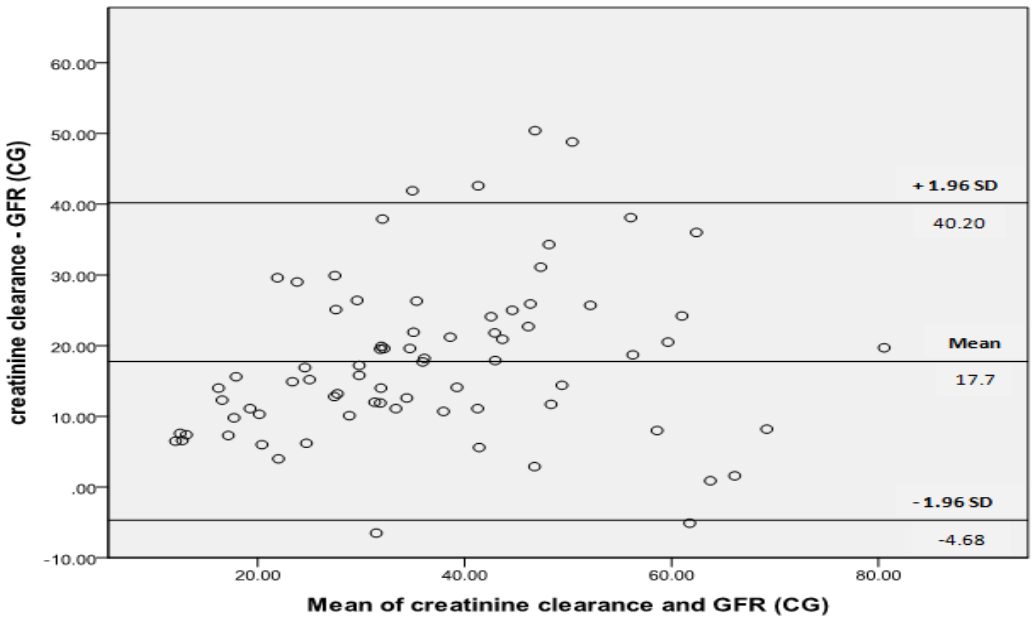

Figure 1. Bland and Altman plots comparing the GFR calculated by the Cockroft-Gault with the GFR estimated by creatinine clearance

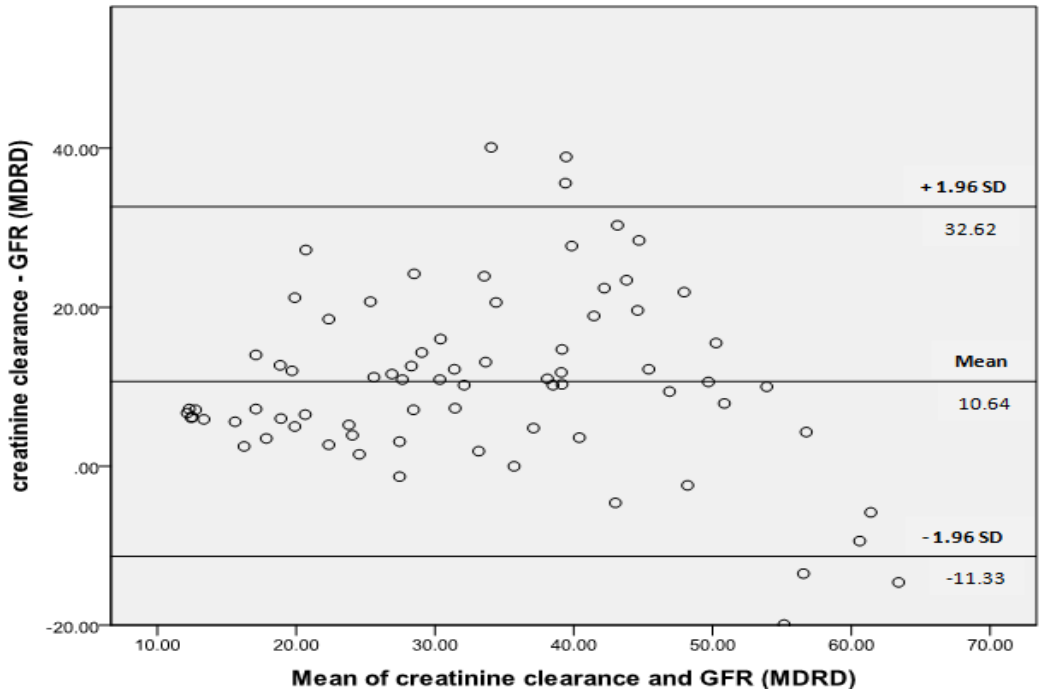

Figure 2. Bland and Altman plots comparing the GFR calculated by the MDRD formula with the GFR measured by the inulin clearance

calculated by CG or MDRD formula correlates well with creatinine clearance in 24-hour urine collection, the MDRD formula is more accurate in stage 3 and 4 CKD patients.

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