InnoVationInfo

Journal of
Biomedical Research and Reviews

ISSN: 2581-7388
Volume 1: 2
J Biomed Res Rev 2018

Comparison between creatinine-based equations among diabetic nephropathy patients

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Abstract

Background: Diabetes is a leading cause of chronic kidney disease (CKD). Using some creatinine-based equations is the most widely distributed method in evaluating the kidney function. it can give an inaccurate estimated result, especially in individuals with typical renal function Modification of Diet in Renal Disease (MDRD) formula, Cockcroft-Gault (CG) equation, and the newly published formula of Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation are widely used during estimation the kidney function practice.

Method: A total of 31 studies have been included in the final review. These studies comparing three creatinine-based formulas (MDRD, CG, And CKD-EPI equations) among diabetic nephropathy (DN) patients. The studies have been downloaded from PubMed, ScienceDirect, and google scholar databases.

Results: CG equation overestimates the renal function among diabetes patients especially in lower glomerular filtration rate (GFR) levels. In addition, the CG equation overestimates the renal function in healthy patients more than the diabetic patients. In contrast, both CKD-EPI and MDRD formulas are underestimating the renal function, especially in higher GFR levels. CKD-EPI formula has been achieved better than MDRD and CG formulas in the renal function estimation. While CG performed better than CKD-EPI and MDRD formulas among obese diabetic nephropathy people.

Conclusion: The estimation of renal function by creatinine-based equation can be overestimated or underestimated the gold standard (mGFR).

Keywords: CG, Cockcroft-gault, Renal function estimation, MDRD, Modification of diet in renal disease, CKD Epidemiology Collaboration, CKD-EPI, Creatinine based equations, Diabetes, Diabetic nephropathy.

Introduction

Diabetic nephropathy (DN) has emerged as a global problem in the community health with growing prevalence [1]. Making matters worse, Diabetes mellitus (DM) is the prime causative for end-stage renal disease (ESRD) and renal failure. Therefore, precise assessment of kidney function among DM patients is needed [2]. There are Numerous equations for estimation the renal function, those equations have been used for glomerular filtration rate (GFR) or creatinine clearance (CrCl) evaluation, However, there is a lack of universality across the multiple clinical situations encountered by the health care providers [3]. Using some creatinine-based equations is the most widely distributed

Article Information

Article Type: Review
Article Number: JBRR113
Received Date: 03 September, 2018
Accepted Date: 05 September, 2018
Published Date: 11 September, 2018

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Citation: Alzaibak MAA, Kassab YW (2018) Comparison between creatinine-based equations among diabetic nephropathy patients. J Biomed Res Rev Vol: 1, Issu: 2 (25-30).

method in evaluating the kidney function. However, it can give inaccurate estimated results, especially in individuals with typical renal function [4]. Creatinine-based equations are regularly performed for estimation the renal function because of being both practical and cheap. These formulas are used for ESRD detecting, monitoring of the disease progression, and prognosis prediction [5]. Modification of Diet in Renal Disease (MDRD) formula, Cockcroft-Gault (CG) equation, and the newly published formula of Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation are widely used during estimation the kidney function practice [6].

Research Methodology

This review article comparing between creatinine-based formulas (MDRD, CKD-EPI, CG equations) among diabetic nephropathy (DN) patients. After searching on online databases (ScienceDirect, PubMed, And Google scholar), 34 studies were found comparing between creatinine-based equations in DN patients. Three studies were excluded because the full text was not in the English language. In the review study, 31 studies were included. All the included studies were in English and published between 2010 and 2018. Keywords (such as diabetes, diabetic nephropathy, CKD, Chronic kidney disease, renal function estimation, glomerular filtration rate, GFR, MDRD, CKD Epidemiology Collaboration, CG, CrCl, Cockcroft-gault, Cr clearance, modification of diet in renal disease, CKD-EPI, Creatinine-based equations) were used with different combinations.

Comparison between MDRD and CKD-EPI Equations

Table 1 shows the comparison between MDRD and CKD-EPI formulas among DN patients.

Discussion

Based on the outcomes of the compared studies among DN patients, CKD-EPI and MDRD equations both of them underestimate the renal function when compared with mGFR standard values [11,14,20]. These equations can enhance the underestimation of the renal function particularly at higher GFR values and chronic kidney disease (CKD) stages [20]. In terms of evaluating the accuracy of the CKD-EPI, CKD-EPI formula has been shown a better accuracy and precision when compared to MDRD study during the estimation of the renal function [17-19]. Furthermore, CKD-EPI formula gave more accurate assessment among healthy patient when compared to DN patients [8].

A new study has been published, check the abilities of both equations in predicting the progression of cardiovascular disease (CVD). This study found that the CKD-EPI equation showed better ability in stratification the CVD risk of all causes and mortality rate [13]. Additional study has been done, showing the abilities of the equations in the prediction of the heart failure risk. The study showed that the CKD-EPI equation confirmed better ability in the risk prediction of the heart failure disease [16].

Finally, CKD-EPI study gave higher eGFR estimates among young DM people when Compared with MDRD equation [9]. Therefore, it leads to the lower prevalence of impaired renal function among DN population and lower prevalence of CKD, that when comparing it with the MDRD [7].

Comparison between MDRD and CG Equations

Table 2 explains the differentiation between MDRD and CG equations among DN patients.

Discussion:

The comparison studies confirmed that CG and MDRD underestimate the renal function (eGFR) in comparison with the golden standard, CrCl measured by using 24 hr urine [23]. In addition, a large study has done on 16,002 patients. That study confirmed that the obtained eGFR values MDRD are higher than those obtained from the CG equation [24]. Finally, the GFR estimates values which are calculated by the CG equation has a smaller variance and standard deviation when compared to the GFR estimates which are calculated by the MDRD equation [22].

Comparison between MDRD, CKD-EPI, and CG Equations

Table 3 shows the studies that compare MDRD, CG, and CKD-EPI equations among DN patients.

Discussion:

Based on the studies result, among DN patients both CKD-EPI and MDRD formulations underestimate the standard values (mGFR) while the CG equation overestimates it. CG equation overestimation increase in lower CKD stages especially in healthy patients [26, 26, 29, 34]. Furthermore, the CG equation showed the lowest levels of estimated GFR (eGFR) when compared with CKD-EPI and MDRD equations [30].

In comparing the obtained values from three equations without using golden standard (mGFR), MDRD and CKD-EPI demonstrated closer eGFR values for each other when compared with CG in DN patients. In addition, CG number of CKD patients was higher than MDRD and CKD-EPI formulas especially in higher CKD stages [6,25,30].

Some studies investigated the performance and the accuracy for all the equations. Those studies found that the estimated GFR values using the CG equation are less accurate than MDRD while CKD-EPI formula has higher accuracy than MDRD equation [4,27,29]. Otherwise, two studies one of them is a large cohort study done on DN patients (n=22,294 T2DM patients) showed that MDRD is more accurate and have better advantages over CG and CKD-EPI equations [26,31].

Although the CG equation did not show a good accuracy and precision among DN patients, it showed a better accuracy in obese DN patients when compared to other equations. Two studies improved that equation achieved slightly better than CKD-EPI and MDRD in estimation the renal function among DM obese patients [32,33].

Conclusion

The measurement of eGFR plays the main role in the

Table 1: Comparison between MDRD and CKD-EPI formulas among DN patients.

Author and year	Patient	Gold standard comparison	Outcomes
Pugliese et al., [7].	N=15,773 type 2 diabetes mellites (T2DM). Mean age: 67 years.	Measured GFR (mGFR) from 24 hr urine.	CKD-EPI study has been given the decreased prevalence of CKD and impaired estimated GFR (eGFR) comparing to the MDRD Study equation. The number of individuals who have impaired eGFR (<60 mL/min/1.73 m2), decreased (8.2% reduction) from 2959 patients (18.7%) to 2715 patients (17.2%) utilizing the CKD-EPI equation instead of the MDRD equation (P=0.0012).
Camargo et al., [8].	N=111 patient. Gender: 51% female.	mGFR has measured by the (51) Cr-EDTA single-injection method.	Among healthy T2DM patients, The CKD-EPI study is less accurate than MDRD. Also, the MDRD equation did not achieve better than the CKD-EPI formula in T2DM patients. During data analysis, we found that the accuracy (P30) was lower for CKD-EPI in DM patients than in healthy volunteers (66 vs 90%, respectively, P < 0.001).
Drion et al., [9].	N=1097 DM patient. Age: from 18 to 92 years.	mGFR from 24 hr urine.	the CKD-EPI formula has given higher eGFR among young DM individuals when Compared with the MDRD formula, causing a lower CKD prevalence in general population.
Vučić et al., [5].	N=842 DM patients. Gender: 48.2% males.	None	CKD-EPI formula might be a better surrogate indicator of GFR in normoalbuminuria and hyperfiltration individuals. There was a good agreement between two equations in normoalbuminuric patients and very good agreement in macro- and microalbuminuric patients. Kappa statistics values in normo- and micro- and macroalbuminuric people were 0.793, 0.909 and 0.947, respectively.
Kumpatla et al., [10].	N=198 DM patients. Gender: 71% males. Age: 55.3 ± 9.8 years	mGFR from 24 hr urine	Both CKD-EPI formula and MDRD formula have underestimated the renal function in one percent and overestimated the renal function in 26.8% of the total studied population (kappa κ=0.60). In addition, CKD-EPI and MDRD showed the smallest mean absolute bias in the study.
Veríssimo et al., [11].	N=354 healthy and DM patients.	mGFR using 51 Cr-GFR* method.	CKD-EPI and MDRD equations systematically underestimated mGFR, and there was no agreement found between mGFR and eGFR (p<0.001). Overall, the mean bias of CKD-EPI and MDRD were 5±23 and 10±25, respectively (p=0.001).
Liu et al., [12].	N=1196 individuals. 589 T2DM patients and 607 non-diabetic patients	mGFR by 99 mTc-DTPA** method.	CKP-EPI equation has been shown a better accuracy when compared with the MDRD. The accuracy for the MDRD equation was 55.2%, and 62.9% for the CKD-EPI formula (P=0.4).
McFarlane et al., [13].	N=109,055 patients. Gender 31.8% male. Age: 55.3 ± 0.05 years Race: 31.8% African American.	none	The CKD-EPI equation showed better ability in stratification the CVD risk of all causes and mortality rate comparing to MDRD equation. The area under curve (AUC) for CVD mortality was 0.737 [0.703–0.771] using eGFR MDRD and they were lower than those obtained by eGFR-CKD-EPI (0.767 [0.736–0.798]) during prediction of CVD mortality.
MacIsaac et al., [14].	N=199 patients. 75 % T2DM	mGFR from 24 hr urine.	MDRD and CKD-EPI equations fundamentally underestimate the mGFR values for an identical extent: bias for MDRD: -11 ± 2.1 ml/min/1.73 m2 (p<0.001) and for CKD-EPI: -12 ± 1.4 ml/min/1.73 m2 (p<0.001).
Cabrerizo et al., [15].	N=425 patients with pluripathology (PP) criteria. Age: 81.7 ± 7.9 years.	none	Regardless of age and gender, the new CKD-EPI formula deteriorates the degree of renal failure. The mean eGFR in women was 5.2 ml/min/1.73 m2 and was lower with the CKD-EPI than with MDRD (p<0.001). Also, the mean eGFR in men was 6.8 ml/min/1.73 m2 and was also lower with the CKD-EPI (p<0.001).
Wang et al., [16].	N=12258 White and 16886 African American T2DM patients age: 30–90 years	none	CKD-EPI equation confirmed better ability in the risk prediction of heart failure disease than MDRD when GFR values were 60 ml/min/1.73 m2 or lower, and even mildly decreased GFR (60–74 ml/min/1.73 m2) the values are correlated with an elevated risk of heart failure.
Lee et al., [17].	N=707 DM patients. Age: 61.9 ± 12.2 years.	mGFR from 24 hr urine.	The CKD-EPI study formula is preferable on the MDRD study formula among T2DM. Among these patients, 15.9% were reclassified to a lower stage of CKD and 0.9% were reclassified to a higher stage of CKD.
Douros et al., [18].	N=2070 participants.	mGFR from 24 hr urine.	CKD-EPI demonstrated higher accuracy than MDRD. The precision for MDRD was 9.4 mL/min/1.73 m2, and 11.0 mL/min/1.73 m2 for CKD-EPI formula. The accuracy for MDRD was 46.0%, and 53.3% for CKD-EPI.
Targher et al., [19].	N=2,823 T2DM patients.	none	the assessment of GFR using the CKD-EPI equation is more appropriately stratifies patients with T2DM. The AUC for CVD mortality was (0.767 [0.736–0.798]) using the CKD-EPI equation were greater than those obtained by using MDRD equation 0.737 [0.703–0.771].
Silveiro et al., [20].	N=105 T2DM patients. Age: 57 ± 8 years. Gender: 50% men	mGFR using	Among T2DM patients, The CKD-EPI and MDRD formulas underestimate mGFR especially at higher GFR values. Bias was 24 and 20 mL/min/1.73m2 for MDRD and CKD-EPI, respectively (P=0.26). Accuracy P30 (95% CI) was 64% (56–75) for MDRD and 67% (58–74) for CKD-EPI.
*51 Cr-GFR: Cr-EDTA single-injection.			
**99 mTc-DTPA: 99mTc-diethylene triamine penta acetic acid.			

Table 2: Differentiation between MDRD and CG equations among DN patients.

Author and year	Patient	Gold standard comparison	Outcomes
Chang Ye [21].	N=294 DM. age: 57.28 ± 13.95 years.	mGFR using 99mTc-DTPA method.	the measurement was smaller in CG formula. Also, when we estimated the renal function by the CG equation in patients with CKD stage 4-5, we get GFR values with a higher compliance rate. In addition, the CG formula had a smaller deviation compared to MDRD In CKD stage 3.
Saha et al., [22].	N=75 T2DM patients with hypertension	CrCl from 24 hr urine.	The eGFR correlation which obtained by using CG method was better than the MDRD method with AER (r=0.89, 0.69, respectively). eGFR by MDRD method has a higher variance and standard deviation when compared with eGFR by CG method.
Al Osali et al., [23].	N=158 DM patients. Age: 61.65 ± 10.46. BMI: 27.93 ± 5.89.	CrCl from 24 hr urine.	CG and MDRD underestimate GFR values in comparison to mGFR. The CG and MDRD correlated significantly with mGFR, with a slightly stronger correlation with MDRD (r=0.658, 0.701 respectively; P <0.001).
Sohn et al., [24].	N=16,002. Gender: 42% male.	None	The eGFR which are derived from MDRD formula was significantly more than those obtained using the CG formula, with a mean difference of 6.7 mL/min ($p < 0.001$). the difference between CG formulas and MDRD equation was obviously larger in older adults.

Table 3: Study of comparison of MDRD, CG, and CKD-EPI equations among DN patients.

author and year	patient	Gold standard comparison	outcomes
Zaman [25].	N=4,042 T2DM patients. Age: 61.4 ± 10.7 years.	none	The CKD-EPI equation CKD subjects number was slightly higher in Stages 4 and 5 when compared with MDRD. However, the frequency of CKD was 1,272 (31.4%) according to the CG equation. Patients with Stage 3 (n=1,040) were higher based on the C-G equation as compared to the MDRD-4 (n=727) and the CKD-EPI equation (n=730).
Fontela et al., [6].	N=146 patients. Gender: 35.6% men. Age: 60.9±8.9 years.	none	CKD-EPI and MDRD studies have shown a greater similarity, and the difference between them was more marked (11%) when compared to the CG formula.
Schwandt et al., [26].	N=22,294 patients with T2DM and 2,222 individuals with T1DM	CrCl from 24 hr urine.	CG overestimates, while CKD-EPI, MDRD underestimate. The highest accuracy (75.3%) was for MDRD equation comparing to other equations. Also, MDRD had the Smallest mean bias ($p < 0.0001$).
Lee et al., [27].	N=6739 Chinese T2DM patients. Gender: 49.7% men. Age: 64.6 ± 12.4 years.	none	MDRD formula discriminated poorly in comparing with CKD-EPI formula (C statistics: MDRD 0.689 vs CKD-EPI 0.714., $p < 0.0001$)
Rognant, et al.,2011 [4].	N=246 DM patients. Gender: 59% of men. Race: 95.1% white. Age: 62.5 ± 13.0 years.	inulin clearance as standard	The study confirms that the MDRD formula is more accurate than CG formula is less accurate. And the CG equation should not be used in evaluating the GFR among DM patients. R2 values for the three equations were 0.814, 0.818, and 0.728 for CKD-EPI, MDRD, and CG respectively.
Fabbian et al., [28].	N=1686 T2DM patients Gender: 57.1% males. Age: 68±10 years.	none	Estimated the renal function with CG formula exhibited a better renal function, and Estimated the renal function with MDRD formula exhibited a worse renal function in the whole population.
Maple et al., [29].	N=564 (224 DM) patients.	mGFR by plasma disappearance of iohexol over 4 hr method.	the CG formula overestimated the standard values by 9.9 ml/min. The CKD-EPI equation achieved better than the MDRD formula in individuals with or without DM. Also, the CKD-EPI equation has been underestimated the standard values by 8.8 and 1.0 ml/min/1.73 m2 at eGFR < 90 and > 90 ml/min/1.73 m2 levels, respectively.
Guo et al., [30].	N=21,723 DM patients. Age: ≥ 60 years.	none	The highest value for eGFR was detected for stage 1 CKD patients, and the lowest eGFR levels were detected using the CG formula (70.20 ± 18.18).
Agoons et al., [31].	N=51 T2DM patients. Age: 57.0±8.3 years.	CrCl from 24 hr urine.	The MDRD formula looks to have the best advantage over CG and CKD-EP in evaluation renal function. GFR from the CrCl, MDRD, CKD-EPI, and CG formulas were Converged (overall P=0.298), and MDRD (r=0.58; 95% CI: 0.36–0.74), CG (r=0.61; 95% CI: 0.39–0.75) and CKD-EPI (r=0.55; 95% CI: 0.33–0.72) demonstrated the modest correlation in comparison with CrCl (all $P < 0.001$).
Resl et al., [32].	N=571 males, 417 females. Age: 61 ± 22 years.	none	Among DM obese patients, CG formula performed a little bit better than the other equations. The other subgroups showed that the eGFR estimated using CG equation did not show a difference with eGFR calculated by MDRD or the CKD-EPI equations.

Drion et al., [33].	N=1,095 DM patients.	CrCl from 24 hr urine.	The accuracy for CG equation was the best (>70.4%) in all BMI categories. In addition, the CG is a better indicator of kidney function than the CKD-EPI and the MDRD in DM individuals. CrCl and CG showed a significant difference, for the CG values ($p<0.001$), and CrCl ($p<0.01$).
Gaspari et al., [34].	449 diabetic patients aged more than 40 years	mGFR with iohexol plasma clearance technique.	The three creatinine-based equations underestimated the renal function. the actual decline with a bias ranging from 2.03 to 4.16 ml/min/1.73m2 per year, mean percent error (MPE) ranged from 52.42 to 129.74%.

monitoring and detection of renal disease among DN patients. Therefore, the estimation of true renal function in the general population plays a significant role. All the studies showed that creatinine-based equations can overestimate or underestimate the gold standard (mGFR) during the estimation of the renal function. The variation in estimates depends on the number of the risk factors for CKD such as age, sex, race, etc. MDRD and CKD-EPI formulas can enhance the underestimation of the renal function particularly at higher GFR values and chronic kidney disease (CKD) stages [20]. While the CG equation overestimates the mGFR especially at lower GFR levels, especially among healthy individuals [22].

In terms of the accuracy and precision, the accuracy of creatinine-based formulas is still unclear. CKD-EPI equation showed a better accuracy than the other equations in most of the studies. Otherwise, a large cohort study (N= 22,294) showed that the MDRD equation showed the highest accuracy compared to the other equations [26]. In contrast, the CG equation did not show a good accuracy in most of the studies but it exhibited a better accuracy on the obese DN patients [32,33].

Compliance with Ethical Standards

Conflict of Interest: Author A declares that he has no conflict of interest. Author B declares that he has no conflict of interest.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

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Citation: Alzaibak MAA, Kassab YW (2018) Comparison between creatinine-based equations among diabetic nephropathy patients. J Biomed Res Rev Vol: 1, Issu: 2 (25-30).