Performance of CKD-EPI versus MDRD among Diabetic Egyptians

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Abstract: Introduction: Early changes in diabetic nephropathy involve increased urinary albumin excretion rate and/or a temporal increase in GFR (hyper-filtration), which are not necessarily inter-related. Current standards of clinical practice include annual measurement of ACR and serum creatinine-estimated GFR for staging of CKD. Objective: The aim was to evaluate performance of The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, modification of diet in renal disease (MDRD) formula in the prediction of glomerular filtration rate (GFR) as compared to renal isotope scan 99m Tc DTPA (TGFR) in diabetic patients with various degrees of albuminuria. Methods: GFR was measured in 52 diabetic patients using Tc99 DTPA renal scan (TGFR), and estimated (eGFR) from standardized creatinine, with MDRD and CKD-EPI equations, and their performance evaluated regarding clinical stages of albuminuria and chronic kidney disease. Results: In a group of 52 diabetic patients (67.3% were females, males were 32.7%) with Mean age was 54.75±12.52 years and mean duration of diabetes 8.87±7.05 years. Among all patients, the estimated bias of eGFR by MDRD than TGFR by isotope scan is -19.80±33.98, while estimated bias of eGFR by CKD-EPI than TGFR by isotope scan is -14.24±15.00 (95% limits of agreement 15.2 – -43.6). In patients with measured GFR ≥60 ml/min, the estimated bias of eGFR by MDRD than TGFR by isotope scan was -38.13±41.46, while estimated bias of eGFR by CKD-EPI than TGFR by isotope scan is -24.01±14.37.The estimated bias of eGFR by MDRD than TGFR by isotope scan in diabetic patients with microalbuminuria was -23.73±37.80, while estimated bias of eGFR by CKD-EPI than TGFR by isotope scan is -15.80±17.39. Conclusion: CKD-EPI equation might be a better tool in estimating GFR in Egyptian patients with microalbuminuria and early stages of CKD in diabetes.
[Khaled Abou-Seif, Yahya Makkeyah, Maha Behairy and Mohamed Mostafa Ali. **Performance of CKD-EPI versus MDRD among Diabetic Egyptians.** *Life Sci J* 2014;11(10):1384-1390]. (ISSN:1097-8135). http://www.lifesciencesite.com. 201. doi:10.7537/marslsj111014.201.

Keywords: GFR, Albuminuria, CKD-EPI, MDRD.

1. Introduction

The National Kidney Foundation (NKF) recommends the use of the Modification of Diet in Renal Disease (MDRD) study equation to estimate glomerular filtration rate (GFR). However, it has been demonstrated that this equation, although reasonably accurate to evaluate the kidney function of patients with chronic kidney disease (CKD), tends to underestimate the GFR in subjects with normal or near-normal renal function, as well as in diabetic patients. [1]

The validity of the MDRD study equation has been challenged in several studies conducted in diabetic patients, with pronounced limitation of the MDRD equation is a systematic underestimation of estimated GFR at higher levels (>60 mL/min/1.73 m^2), which might particularly compromise its suitability in patients with incipient kidney disease and hyperfiltration. [2]

For this reason, a new equation, the CKD-Epidemiology Collaboration (CKD-EPI) equation, was developed and the initial analyses have demonstrated the improved accuracy of GFR estimation with the new formula, which could eventually replace the MDRD equation for routine clinical use. However, it remains to be determined whether the CKD-EPI equation will work equally well in all populations. [3]

American Diabetes Association (ADA) recommends measuring serum creatinine at least annually in all adults with diabetes regardless, of the degree of urine albumin excretion. Serum creatinine should be used to estimate GFR and to stage the level of CKD, if present. Estimated GFR can be estimated using formulae such as MDRD equation or CKD-EPI the equation. [4]

In this study we aimed to compare the performance of (CKD-EPI) and (MDRD) equations in estimating GFR in diabetic patients with various degrees of albuminuria.

2. Material and Methods

This cross sectional study was conducted on 52 diabetic patients from Ain Shams University Hospitals, Cairo, Egypt. All patients were older than 18 years with established diagnosis of diabetes mellitus (DM) regardless the type and treatment. Patients with ESRD on dialysis, fever, urinary tract infection, hematuria, or nephrotic range proteinuria were excluded from the study. Informed consent was

obtained from each participant. All patients were subjected to history taking and clinical examination including age, sex, duration of DM and known comorbid conditions. Body mass index (BMI) & Mean arterial blood pressure (MAP) were calculated. A fasting blood sample was taken for laboratory tests (Creatinine, albumin, HbA1c). Creatinine was measured in serum using liquicolor Jaffé-Reaction Photometric Colorimetric Test for Kinetic Measurements. Fresh, mid-stream urine was collected from all patients and refrigerated at -20˚C. Using Bayer CLINITEK Microalbumin Reagent Strips, a semi quantitative method for Microalbuminuria, analysis was done using the CLINITEK Analyzer. According to the manufacturer, the Bayer Microalbustix test has a sensitivity of 90% and a specificity of 88% for the albumin/creatinine ratio.

Isotope GFR was measured by renal isotope scan 99m Tc DTPA (TGFR). Thirty minutes before the scintigram, patients were instructed to ingest 500 mL of water. Then, patients lay in a supine position on the table of a single-headed gamma camera (Argus, ADAC/Philips). The camera detector was located below the table 30 cm from the patient. A cold vial of commercial DTPA (TechneScan® DTPA, Mallinckrodt) was reconstituted with Tc-99m pertechnetate (chemical impurity <10 µg Al/mL Tc-99m, radiochemical purity >95 %) that was eluted out of the Mo-99/Tc-99m generator (Technetium-99m Generator, Samyoung Unitech), yielding Tc-99m DTPA. A butterfly needle was first inserted into an antecubital vein in an upper extremity, and then Tc-99m DTPA (185 MBq) was injected. Without delay, 10 mL of normal saline was rapidly flushed into the vein. Injected radioactivity was defined as the difference between pre- and post-injection counts, measured in counts per second.

The estimated GFR (eGFR) was calculated as follows:

eGFR (CKD-EPI) = 141 x min (Scr/κ, 1)$^{\alpha}$ x max (Scr/κ, 1)$^{-1.209}$ x $^{0.993}$Age x 1.018 [if female] x 1.159 [if black].[5] Where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κor 1, and max indicates the maximum of Scr/κ or 1.

eGFR (MDRD)= 175 x (serum creatinine $^{-1.154}$) x (age$^{-0.203}$) x 1.212 (if black) x 0.742 (if female). [6]

KDIGO's grading was using for staging the patients into the different CKD stages (KDIGO 2013): G1: >= 90 ml/min/m2, G2: 60-89 ml/min/m2, G3a:45-59 ml/min/m2, G3b:30-44 ml/min/m2, G4: 15-29 ml/min/m2, G5: <15 ml/min/m^2.

Data was analyzed on an IBM personal computer, using IBM SPSS Statistics version 21 software. Data were described as mean± standard deviation (SD) for quantitative (Numerical) variables and as frequency & percentage for qualitative (Categorical) variables. One sample t test was used for comparison of the difference between the various methods of GFR estimation in comparison to the 99m Tc DTPA GFR (TGFR) measured by isotope scan (i.e. gold standard) considering in the null hypothesis that the difference is zero. Bland-Altman plot was to evaluate the agreement between methods for estimating and measuring GFR. Correlation between continuous parametric variables was performed using Pearson correlation coefficient, and correlation between continuous non-parametric variables was performed using spearman correlation coefficient. One-sample t test was performed for testing the difference (estimated bias) between eGFR (using both equations MDRD & CKD-EPI respectively) and TGFR (using isotope scan) assuming in the null hypothesis that the difference is zero i.e. when there is no significant difference means that there is perfect match.

3. Results

This study included 52 diabetic patients from Ain Shams University hospital. Mean age was 54.75±12.52 years. A total of 67.3% of studied population were females, males were 32.7%. As a whole, the mean BMI was 29.65±5.37. Duration since diagnosis of diabetes was 8.87±7.05 years. Regarding the MAP of our patients, the mean was 97.79±15.23 mmHg. Depending on the history taken, 51.9% of our patients were known hypertensive, and 17.3% had positive history of ischemic heart disease. The measured albumin creatinine ratio ranged from 5 to 1500 mg/g with mean 486.25±545.90.

There was a statistically significant positive correlation between both equations to estimate GFR and TGFR measured by isotope scan, with higher r value for the correlation between eGFR (CKD-EPI) & TGFR versus the correlation between eGFR (MDRD) & TGFR among all patients (0.958 vs 0.856), among patients with TGFR <60ml/min (0.917 vs 0.916), among patients with TGFR ≥60ml/min (0.72 vs 0.517), among microalbuminuric patients (0.935 vs 0.803), and among macroalbuminuric patients(0.992 vs 0.909). (Table 4, Figure 1).

Among all patients, the estimated bias of eGFR by MDRD than TGFR by isotope scan is -19.80±33.98, while estimated bias of eGFR by CKD-EPI than TGFR by isotope scan is -14.24±15.00 (95% limits of agreement 15.2 – -43.6).

Correlation of eGFR by CKD-EPI equation was significant with age (r=-0.292,P < 0.05), MAP (r=-0.350, P < 0.05), and highly significant with A/C ratio ((r=-0.422, P < 0.01). while, Correlation of

eGFR by MDRD equation was very highly significant with MAP (r=-0.470, $P < 0.0001$), and highly significant correlation with A/C ratio (r=-0.377, $P < 0.01$).

Using one sample t test, there was no statistical significance regarding the mean difference between eGFR (MDRD) & TGFR compared to zero value among macroalbuminuric patients (P value=0.054), and patient with measured GFR <60 ml/min (P value = 0.06); while there was a statistical significance regarding the mean difference between eGFR (MDRD) & TGFR among all patients, microalbuminuric patients and patients with measured GFR ≥60 ml/min.

Also, when using one sample t-test, there was a statistical significance regarding the mean difference between eGFR (CKD-EPI) & TGFR compared to zero value among all patients, patients with measures GFR <60ml/min, patients with measured GFR ≥60 ml/min, microalbuminuric patients, and macroalbuminuric patients.

Table (1) Studied variables among all patients (n=52)

Studied variables	Mean±SD	Median (min-max)
Age	54.75±12.53	57.50 (21.0-74.0)
Duration	8.87±7.05	7.50 (0.0-30.00)
BMI	29.65±5.38	30.86 (18.75-41.52)
Systolic BP	131.15±19.47	130.0 (90.00-170.0)
Diastolic BP	81.15±14.37	80.0 (60.00-100.0)
Mean Arterial Pressure	97.79±15.24	100.0 (70.0-123.0)
S.Creatinine	1.54±1.54	0.90 (0.30-8.10)
S.Albumin	3.12±0.73	3.20 (1.50-5.10)
HbA1c	9.91±1.58	9.90 (7.50-13.20)
Urinary A/C ratio (mg/gm)	486.25±545.90	300.0 (5.0-1500.0)

Table (2) GFR by different methods among the studied patients

GFR		Mean± SD
All patients (n=52)	TGFR (Isotope)	57.20±29.81
	eGFR (MDRD)	77.00±55.80
	eGFR (CKD-EPI)	71.44±40.91
<60 ml/min (n=27)	TGFR (Isotope)	32.43±16.52
	eGFR (MDRD)	35.26±18.62
	eGFR (CKD-EPI)	37.63±20.66
≥60 ml/min (n=25)	TGFR (Isotope)	83.95±12.52
	eGFR (MDRD)	122.08±46.53
	eGFR (CKD-EPI)	107.96±20.46
Microalbuminuric (n=29)	TGFR (Isotope)	67.54±24.87
	eGFR (MDRD)	91.28±54.72
	eGFR (CKD-EPI)	83.34±38.27
Macroalbuminuric (n=19)	TGFR (Isotope)	36.79±26.58
	eGFR (MDRD)	50.11±50.14
	eGFR (CKD-EPI)	47.63±32.33

Table (3) Correlation of different methods of estimating GFR with TGFR measured by isotope scan

		Correlation with TGFR	
		r value	*P* value
All patients (n=52)	eGFR (MDRD)	0.856	0.000
	eGFR (CKD-EPI)	0.958	0.000
<60 ml/min (n=27)	eGFR (MDRD)	0.916	0.000
	eGFR (CKD-EPI)	0.917	0.000
≥60 ml/min (n=25)	eGFR (MDRD)	0.517	0.000
	eGFR (CKD-EPI)	0.720	0.000
Microalbuminuric (n=29)	eGFR (MDRD)	0.803	0.000
	eGFR (CKD-EPI)	0.935	0.000
Macroalbuminuric (n=19)	eGFR (MDRD)	0.909	0.000
	eGFR (CKD-EPI)	0.992	0.000

Table (4): Comparison between the mean difference between estimated GFR (using CKD-EPI & MDRD) and TGRF using isotope scan (using one-sample T test)

Difference in GFR		Mean± SD	95% CI of mean		*P* value
All patients (n=52)	TGFR (Isotope)-eGFR (MDRD)	-19.80±33.98	-29.26	-10.34	0.000
	TGFR (Isotope)-eGFR (CKD-EPI)	-14.24±15.00	-18.42	-10.06	0.000
<60 ml/min (n=27)	TGFR (Isotope)-eGFR (MDRD)	-2.83±7.48	-5.78	0.13	0.060
	TGFR (Isotope)-eGFR (CKD-EPI)	-5.20±8.61	-8.60	-1.79	0.004
≥60 ml/min (n=25)	TGFR (Isotope)-eGFR (MDRD)	-38.13±41.46	-55.24	-21.01	0.000
	TGFR (Isotope)-eGFR (CKD-EPI)	-24.01±14.37	-29.94	-18.08	0.000
Microalbuminuric (n=29)	TGFR (Isotope)-eGFR (MDRD)	-23.73±37.80	-38.11	-9.36	0.002
	TGFR (Isotope)-eGFR (CKD-EPI)	-15.80±17.39	-22.42	-9.19	0.000
Macroalbuminuric (n=19)	TGFR (Isotope)-eGFR (MDRD)	-13.32±28.22	-26.92	0.29	0.054
	TGFR (Isotope)-eGFR (CKD-EPI)	-10.84±6.83	-14.13	-7.55	0.000

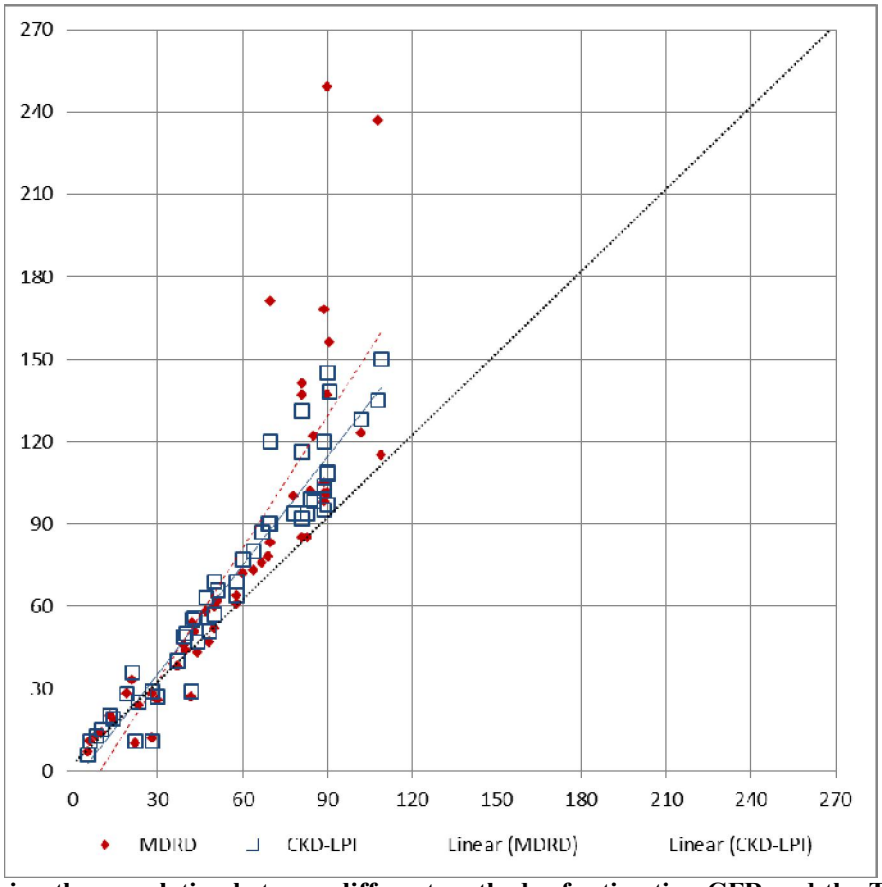

Figure (1): Showing the correlation between different methods of estimating GFR and the TGFR measured using isotope scan. Note the reference line (black dotted) that represents the perfect agreement between the methods to estimate the GFR with the measured GFR by isotope.

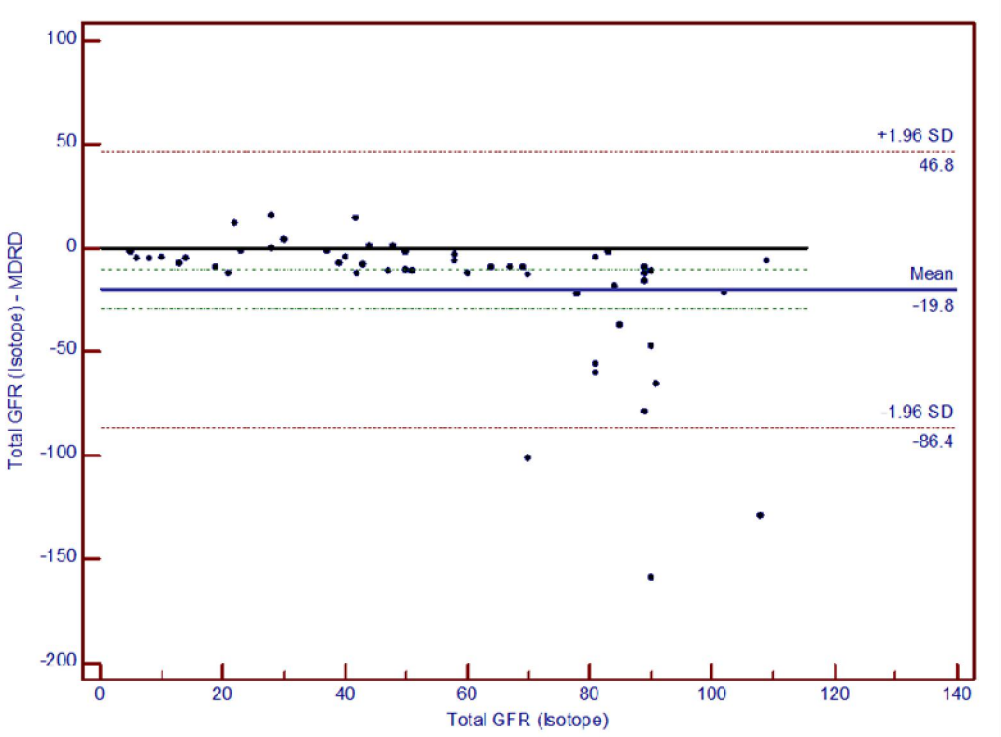

Figure (2): Bland-Altman plot for the difference between the estimated GFR using MDRD and measured GFR using isotope scan, taking the total GFR measure by isotope scan as the X-axis of the chart (i.e. gold standard)

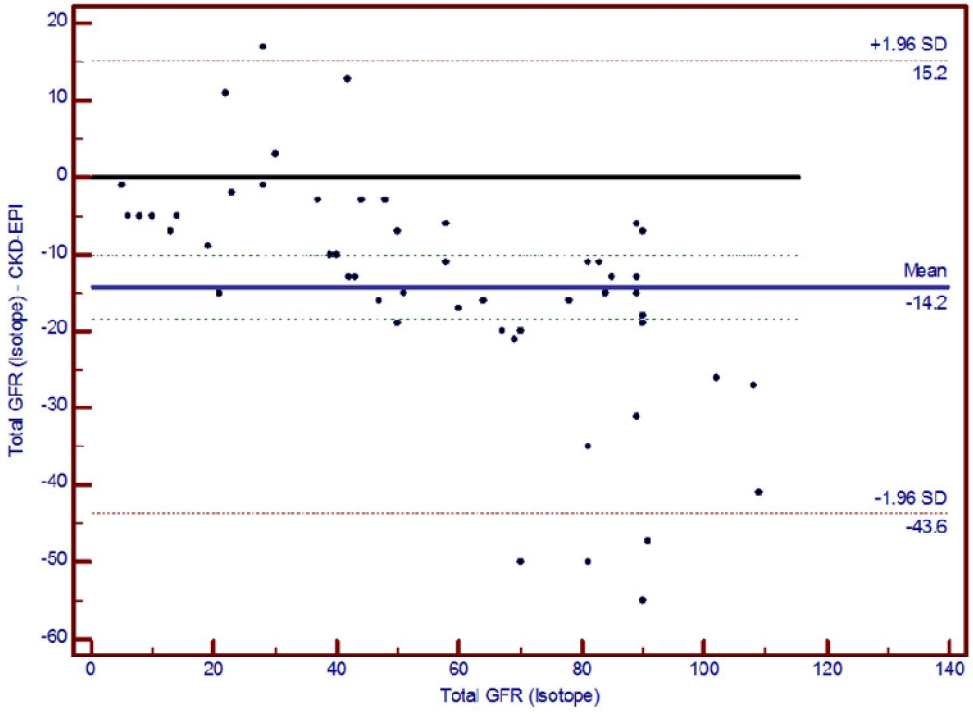

Figure (3): Bland-Altman plot for the difference between the estimated GFR using CKD-EPI and measured GFR using isotope scan, taking the total GFR measure by isotope scan as the X-axis of the chart (i.e. gold standard)

When using Bland-Altman plot, Among patients with measured GFR <60 ml/min, the estimated bias of eGFR by MDRD than TGFR by isotope scan is -2.83±7.48, while estimated bias of eGFR by CKD-EPI than TGFR by isotope scan is -5.20±8.61.Among patients with measured GFR ≥60 ml/min, the estimated bias of eGFR by MDRD than TGFR by isotope scan is -38.13±41.46, while estimated bias of eGFR by CKD-EPI than TGFR by isotope scan is -24.01±14.37.

Among microalbuminuric patients, the estimated bias of eGFR by MDRD than TGFR by isotope scan is -23.73±37.80, while estimated bias of eGFR by CKD-EPI than TGFR by isotope scan is -15.80±17.39. Among macroalbuminuric patients, the estimated bias of eGFR by MDRD than TGFR by isotope scan is -13.32±28.22, while estimated bias of eGFR by CKD-EPI than TGFR by isotope scan is -10.84±6.83.

4. Discussion

According to ADA guidelines for prevention and management of diabetes complication, recommends that serum creatinine should be used to estimate GFR and to stage the level of CKD, if present. According to the guidelines, the eGFR can be estimated using formulae such as the MDRD equation or the CKD-EPI equation.[4]

Although evaluation of GFR is crucial for CKD diagnosis and staging, different creatinine based GFR estimating equations may misclassify diabetic patients.[7]

In our study, GFR calculated by both CKD-EPI and MDRD formula correlated well with GFR measured by isotope scan. However, CKD-EPI showed better correlation with isotope GFR than MDRD formula in Egyptian diabetic patients.

We found that estimated bias of eGFR by CKD-EPI than TGFR by isotope scan is lower in diabetic patients with GFR> 60 ml/min and diabetic CKD patients with microalbuminuria when compared to estimated bias of eGFR by MDRD than TGFR by isotope scan in those patients; thus, CKD-EPI formula better to be used in predicting early CKD staging in diabetic patients.

Levey's original study, to develop the CKD-EPI, where the equation development was done in 10 studies (n = 8254, 29% with diabetes), and validation in 16 studies (n = 3896, 30 % with diabetes), also the study stated that the equation was more accurate in early CKD (i.e. GFR ≥60 ml/min/m^2) and our study proves the same results in diabetic patients.[5]

Jeong *et al.* study, where the accuracy of the two equations was not significantly different in patients with mGFR <60 mL/min/1.73m^2; however, the accuracy of the CKD-EPI equation was significantly higher than that of the MDRD study equation in patients with GFR ≥60 mL/min/1.73m^2.[8]

Stevens *et al.* subsequently published the description of the CKD-EPI equation validation as well as the development of alternative equations, incorporating diabetes, weight and transplant as additional predictor variables.[9, 10]

It was observed that the addition of these variables did not significantly improve the equation performance. Several studies suggested that CKD-EPI is more accurate in estimating the GFR compared to MDRD in diabetic patients, others however, showed that the bias of both equations was significantly higher in patients with diabetes when compared with healthy volunteers.[11]

Although eGFR by CKD-EPI in our diabetic patients was better correlated to TGFR by isotope scan, both formulae (MDRD &CKD-EPI) didn't show perfect agreement with TGFR by Bland-Altman analysis.

Also, There was no statistical significance between eGFR (MDRD) & TGFR among macroalbuminuric patients and among patient with measured GFR <60 ml/min, and the estimated bias of eGFR by MDRD than TGFR was less than bias of CKD-EPI in those patients, which indicates that MDRD formula is better than CKD-EPI in estimating GFR in late stages of diabetic CKD and diabetic patients with macroalbuminuria.

This disappointing performance seems to be associated with specific characteristics of the patients with diabetes, such as hyperglycemia, glomerular hyperfiltration, and obesity, which probably highlight the limitations of creatinine itself as a GFR marker. Hyperglycemia may interfere in two ways. First, it has long been known that glucose levels above 300 mg/dL may affect the performance of the Jaffe reaction to measure creatinine. [12] Another possible explanation could be the hyperglycemia-induced glomerular hyperfiltration and the inability of creatinine to detect this typical phenomenon of diabetes.[13]

Silveiro *et al.* study found that the poor performance of the formulas was further expressed in the chronic kidney disease misclassification of diabetic patients in 8 and 10% of the cases when using the CKD-EPI and MDRD equations, respectively.[14]

In this study, the CKD-EPI and MDRD show high significant correlation with the albumin creatinine ratio. Trimarchi *et al.* found in a recent study a very high statistical significance relation between albuminuria and CKD-EPI.[15] However, some studies have found decreased GFR in the

absence of increased urine albumin excretion in a substantial percentage of adults with diabetes.[16]

Lovrenčić *et al.* found Patients with normoalbuminuria had higher eGFR when calculated by CKD-EPI, than MDRD-Study equation, which significantly influenced the prevalence of stage 1 CKD. There were no differences between the eGFR values derived by two equations in patients with micro and macroalbuminuria, and more advanced staging of CKD.[2]

The cross sectional study, small number of patients and small number of patients with normoalbuminuria are limitations of our study, further cohort study may be needed. In conclusion, the CKD-EPI equation seems to perform better than the MDRD equation in diabetic patients especially early stages of CKD and patients with microalbuminuria.

References

1. Soares AA, Eyff TF, Campani RB, *et al.* Glomerular filtration rate measurement and prediction equations. Clin Chem Lab Med 2009;47(9):1023-32.
2. Vucic Lovrencic M, Radisic Biljak V, Bozicevic S, *et al.* Estimating glomerular filtration rate (GFR) in diabetes: the performance of MDRD and CKD-EPI equations in patients with various degrees of albuminuria. Clin Biochem 2012;45(18):1694-6.
3. Soares AA, Eyff TF, Campani RB, *et al.* Performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study equations in healthy South Brazilians. Am J Kidney Dis 2010;55(6):1162-3.
4. Standards of medical care in diabetes--2014. Diabetes Care 2014;37 Suppl 1:S14-80.
5. Levey AS, Stevens LA, Schmid CH, *et al.* A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150(9):604-12.
6. Levey AS, Bosch JP, Lewis JB, *et al.* A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130(6):461-70.
7. Pugliese G, Solini A, Bonora E, *et al.* The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation provides a better definition of cardiovascular burden associated with CKD than the Modification of Diet in Renal Disease (MDRD) Study formula in subjects with type 2 diabetes. Atherosclerosis 2011;218(1):194-9.
8. Jeong TD, Lee W, Chun S, *et al.* Comparison of the MDRD study and CKD-EPI equations for the estimation of the glomerular filtration rate in the Korean general population: the fifth Korea National Health and Nutrition Examination Survey (KNHANES V-1), 2010. Kidney Blood Press Res 2013;37(4-5):443-50.
9. Stevens LA, Schmid CH, Greene T, *et al.* Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study equations for estimating GFR levels above 60 mL/min/1.73 m2. Am J Kidney Dis 2010;56(3):486-95.
10. Stevens LA, Schmid CH, Zhang YL, *et al.* Development and validation of GFR-estimating equations using diabetes, transplant and weight. Nephrol Dial Transplant 2010;25(2):449-57.
11. Camargo EG, Soares AA, Detanico AB, *et al.* The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is less accurate in patients with Type 2 diabetes when compared with healthy individuals. Diabet Med 2011;28(1):90-5.
12. Husdan H, Rapoport A. Estimation of creatinine by the Jaffe reaction. A comparison of three methods. Clin Chem 1968;14(3):222-38.
13. Silveiro SP, Friedman R, Gross JL. Glomerular hyperfiltration in NIDDM patients without overt proteinuria. Diabetes Care 1993;16(1):115-9.
14. Silveiro SP, Araujo GN, Ferreira MN, *et al.* Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation pronouncedly underestimates glomerular filtration rate in type 2 diabetes. Diabetes Care 2011;34(11):2353-5.
15. Trimarchi H, Muryan A, Toscano A, *et al.* Proteinuria, (99m) Tc-DTPA Scintigraphy, Creatinine-, Cystatin- and Combined-Based Equations in the Assessment of Chronic Kidney Disease. ISRN Nephrol 2014;2014:430247.
16. Kramer HJ, Nguyen QD, Curhan G, *et al.* Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. JAMA 2003;289(24):3273-7.

9/26/2014