C hronic kidney disease (CKD) is a growing major health concern worldwide and is the major cause of end-stage renal disease (ESRD). It carries high risk of cardiovascular events and mortality.¹² Early detection and intensive care can slow the progression of ESRD. Glomerular filtration rate is a surrogate of kidney function. Measurement of true GFR using inulin clearance or radioisotopes is almost impossible
CKD-EPI AND MDRD EQUATIONS

in either clinical practice or research studies and is expensive, time consuming, and requires hospitalization. Predictive equations provide a rapid and convenient method of assessing GFR.3,4 But none are currently ideal and suitable for all ethnic groups, gender, age, and weight variations.

Modification of Diet in Renal Disease (MDRD), cystatin C and creatinine are commonly used predictive equations.5 Recently, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) published an equation for estimation of GFR using age, gender, race and serum creatinine that was found to be more accurate.4,5 CKD is common in Saudi Arabia, with a prevalence rate of 5.7%.7 The aim of this study was to validate the CKD-EPI and MDRD equations in diverse clinical subsets by comparison with GFR measured by inulin clearance.

PATIENTS AND METHODS

The present study was a cross-sectional study conducted in 31 Saudi adults with chronic kidney disease following the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for qualification of CKD with renal transplant.8 The study is a re-analysis of our previous study conducted in 2009.9 It was performed from January 2014 to June 2014 in affiliation with King Saud University in Riyadh, Saudi Arabia by reevaluating the data using the old CKD and MDRD formula compared with the new CKD-EPI formula.3,5,8

- **MDRD equation:**
  \[
  \text{GFR}=1.86 \times (\text{SCR})^{-1.154} \times \text{Age}^{-0.203} \times 0.742 \quad [\text{if female}]
  \]

- **CKD-EPI creatinine equation:**
  \[
  \text{GFR}=141 \times \min \left( \frac{\text{SCR}}{1}, 1 \right) \times \max \left( \frac{\text{SCR}}{1}, 1 \right)^{1.209} \times 0.993^{\text{Age}} \times 1.018 \quad [\text{if female}]
  \]

- **CKD-EPI cystatin C equation:**
  \[
  \text{GFR}=133 \times \min \left( \frac{\text{Scys}}{0.8}, 1 \right)\times \max \left( \frac{\text{Scys}}{0.8}, 1 \right)^{1.329} \times 0.996^{\text{Age}} \times 0.932 \quad [\text{if female}]
  \]

- **CKD-EPI creatinine-cystatin C equation:**
  \[
  \text{GFR}=135 \min \left( \frac{\text{SCR}}{1}, 1 \right) \times \max \left( \frac{\text{SCR}}{1}, 1 \right)^{1.041} \times \min \left( \frac{\text{Scys}}{0.8}, 1 \right)^{0.375} \times \max \left( \frac{\text{Scys}}{0.8}, 1 \right)^{0.211} \times 0.995^{\text{Age}} \times 0.969 \quad [\text{if female}]
  \]

The National Kidney Foundation (NKF) considers a normal GFR value to be 90-120 mL/min/1.73 m². An eGFR below 60 mL/min/1.73 m² suggests kidney damage.1,3,8

Inclusion criteria were that subjects be Saudi adults of either gender and older than 18 years of age. Exclusion criteria were acute renal failure, heart failure, pregnancy, malignancy, or infection. Thirty-one patients gave consent to participate in data collection. The eight patients were recently transplanted (6 months to 9 months), medically stable for more than 6 months, had stable renal function for 3 months and were using transplant medications (prednisone, azathioprine or mycophenolate mofetil and cyclosporine or tacrolimus).

In all subjects, blood samples were drawn for estimation of serum creatinine, fasting blood sugar, and other biochemistry tests for auto-analysis in the clinical laboratory of King Khalid University Hospital, Riyadh, which is accredited by the College of American Pathology and Clinical Laboratory Improvement Amendments (CLIA). Serum creatinine was analyzed using Jaffe’s method which was standardized to isotope dilution mass spectrometry. Serum cystatin C was measured by nephroimmunoassay, which is described in our previous article,7 using the third generation automatized Dimension RxL Integrated Chemistry analyzer (Dade Behring) and commercially available assay kits. An inulin clearance test was also performed as reported previously.9 Patients gave informed consent to participate and were not exposed to any risks or hazards. All procedures were in accordance with the ethical standards and approved by the Institutional Review Board, Deanship of Scientific Research of King Saud University.

SPSS version 17 was used for statistical analysis (SPSS illinois Chicago USA, https://goo.gl/G0S4LT). Quantitative variables are expressed as mean and standard deviation. Pearson correlation and paired t test samples were used to compare the predictive equations with inulin, and the Wilcoxon signed-rank test was used to measure small samples. The Bland-Altman plot and regression analysis were used to evaluate the accuracy and bias of paired sample tests. The mean difference in the Bland-Altman plot is the estimated bias, and the standard deviation of the differences measures the random fluctuations around this mean. Statistical significance was a P value <.05.

### Table 1. The clinical characteristics of study participants.

| Variable          | Mean (SD)   | Range  |
|-------------------|-------------|--------|
| Age               | 42.26 (15.45)| 19-74  |
| Male              | 19          |        |
| Height (cm)       | 160.58 (10.6)| 134-178|
| Weight (kg)       | 68.76 (18)  | 42.6-131.7|
| BSA (m²)          | 1.73 (0.23) | 1.35-2.5|
| Serum creatinine  | 199.8 (164.15)| 51-815 |

BSA-body surface area.
RESULTS
There were 31 participants, (23 CKD and 8 transplant patients, with 19 males) with a mean age of 42.26 (15.21) years and mean weight of 68.76 (18) kg (Table 1). GFR inulin was 51.54 (33.8) mL/min/1.73 m², GFR MDRD was 48.35 (31.5) mL/min/1.73 m², GFR CKD-EPI creatinine was 52.61 (34.39) mL/min/1.73 m², GFR cystatin C was 41.39 (30.02) mL/min/1.73 m², and GFR CKD cystatin C and creatinine was 45.0 (30.9) mL/min/1.73 m² (Table 2). Comparison of estimated GFR by the predictive equations with GFR measured by inulin clearance (a highly accurate measure of GFR), under the subsets of age, gender, BMI, CKD and kidney transplant are shown in Table 2. In contrast to other predictive equations, eGFR CKD-EPI creatinine was closer to the inulin clearance and the difference between GFR inulin and eGFR CKD-EPI creatinine was statistically insignificant in all CKD patients, and in transplant patients, as well as by gender, age, and BMI. The MDRD equation appeared to underestimate GFR. Table 3 shows the correlation of GFR measured by inulin clearance with predictive equations. MDRD and CKD-EPI creatinine were less advantageous compared with CKD-EPI cystatin C and CKD-EPI cystatin-creatinine. Figure 1 shows the linear relationship between inulin clearance and CKD-EPI creatinine (y=0.9537x + 1.367, r²=0.9391). Figure 2 shows the linear relationship between the MDRD formula and inulin clearance (y=1.0464x + 0.9481, r²=0.95). The Bland-Altman plot and regression analysis was performed to compare the relative performance of all the predictive equations by comparing with GFR measured by inulin clearance. When the difference in GFR values by the inulin clearance versus each of the four methods was compared with the null hypothesis of no difference (zero), the difference between GFR by inulin clearance versus three

| Table 2. Table 2. Mean and standard deviation for GFR by inulin clearance compared with estimated GFR by predictive equations in different subsets. |
|---------------------------|-------------------|----------------|-------------------|-------------------|-------------------|-------------------|
|                          | CKD-EPI creatinine | MDRD            | CKD-EPI cystatin C | CKD-EPI cystatin C |
|                          | Mean (SD)         | Mean (SD)       | Mean (SD)         | Mean (SD)         | Mean (SD)         |
|                          | Inulin Clearance  | P value         | P value           | P value           | P value           |
| Total patients           | 51.54 (33.8)      | 52.61 (34.39)   | .490              | 48.35 (31.5)      | .028              |
| CKD patients (23)        | 46.3 (35.6)       | 47.6 (35.9)     | .499              | 44.2 (33.4)       | .22               |
| Transplant patients (8)  | 66.6 (23.7)       | 67 (26.5)       | .874              | 60.25 (23.2)      | .025              |
| Male patients (n=19)     | 58.5 (32.8)       | 58.3 (34.8)     | .9                | 53.5 (31)         | .008              |
| Female patients (n=12)   | 40.6 (34)         | 43.6 (33)       | .213              | 40.2 (31.6)       | .88               |
| <40 years (n=12)         | 60.5 (35)         | 64.8 (36)       | .202              | 58.5 (33)         | .459              |
| 40–60 years (n=14)       | 48 (35.6)         | 47.6 (35.7)     | .736              | 44 (33)           | .032              |
| >60 years (n=5)          | 39.6 (25)         | 37.2 (18)       | .538              | 36.0 (16.3)       | .427              |
| BMI <30 kg/m² (n=23)     | 52.6 (35)         | 53.8 (36)       | .423              | 49.7 (34)         | .03               |
| BMI ≥30 kg/m² (n=8)      | 48.5 (31.8)       | 49 (28.06)      | .907              | 44.38 (24.4)      | .363              |

Units are mL/min/1.73 m²
methods (MDRD formula, CKD-EPI cystatin and CKD cystatin-creatinine) were statistically significant. With the CKD-EPI creatinine method, the difference was not statistically significant compared with the values by the inulin clearance method. This indicates significant agreement between inulin clearance and the CKD-EPI creatinine methods. The Bland-Altman plot also showed a bias of 1.07 with 95% confidence interval (-2.05, 4.19) which indicates good agreement between inulin clearance and the CKD-EPI creatinine methods when compared the bias of other methods as shown in Table 4. The standard deviation of the precision was 8.50 and the limits of agreement of these two methods are -15.60, 17.74. From the Bland-Altman plot, the equal distribution of values around the mean indicates that the two tests produce similar results (the average difference is close to zero). To assess proportional bias, the regression between the difference of GFR between these two methods (CDK-EPI creatinine and MDRD) and the mean GFR of these two methods showed a non-significant proportional bias (b=-0.16, t=-0.35, P=.730).

Table 3. Correlation between glomerular filtration rate equations and inulin clearance test in various clinical subgroups.

| Patient’s category | GFR CKD-EPI cystatin vs. GFR Inulin | GFR MDRD vs. GFR Inulin | GFR cystatin vs. GFR Inulin | GFR CKD cystatin creatinine vs. GFR Inulin |
|--------------------|------------------------------------|------------------------|-----------------------------|------------------------------------------|
| Kidney transplant  | 0.963 .001                         | 0.964 .001             | 0.442 .132                  | 0.793 .009                                |
| CKD patients       | 0.968 .001                         | 0.975 .001             | 0.946 .001                  | 0.973 .001                                |
| Male               | 0.968 .001                         | 0.976 .001             | 0.822 .001                  | 0.928 .001                                |
| Females            | 0.972 .001                         | 0.974 .001             | 0.978 .001                  | 0.984 .001                                |
| Age <40 years      | 0.952 .001                         | 0.966 .001             | 0.811 .001                  | 0.924 .001                                |
| Age >60 years      | 0.979 .001                         | 0.985 .001             | 0.993 .001                  | 0.989 .001                                |
| BMI <30 (kg/m²)    | 0.980 .001                         | 0.986 .001             | 0.853 .001                  | 0.934 .001                                |
| BMI >30 (kg/m²)    | 0.932 .001                         | 0.942 .001             | 0.953 .001                  | 0.969 .001                                |
| Overall            | 0.969 .001                         | 0.975 .001             | 0.863 .001                  | 0.939 .001                                |
| Age 40-60 years    | 0.990 .001                         | 0.986 .001             | 0.877 .001                  | 0.944 .001                                |

Values are ml/min/1.73 m².

DISCUSSION

GFR estimation is mandatory for evaluation of renal function in transplanted kidney patients and in staging of CKD. Since GFR predictive equations are not perfect and their performance is affected by age, gender, ethnicity, BMI and clinical category of the patient, it is

Figure 1. Correlation of eGFR determined by CKD-EPI creatinine and GFR measured by inulin clearance.
therefore necessary to evaluate the performance of estimated GFR predictive equations in order to determine the selection of a most appropriate simple and most applicable equation for GFR estimation in a Saudi population. In our previous study that compared the MDRD and Cockcroft-Gault serum and reciprocal serum cystatin C equations to inulin clearance, we found that MDRD had a strong correlation with inulin clearance.9

A recent study found that in a Saudi population, CKD-EPI creatinine was most appropriate, most accurate, and had less bias in estimating GFR as compared to conventional GFR estimating equations (MDRD, CKD-EPI cystatin C, and CKD-EPI cystatin C-creatinine). Other studies have also reported that the CKD-EPI creatinine equation has better performance in other ethnic populations with different clinical presentations. Levey et al showed that CKD–EPI creatinine is more accurate, precise and had less bias compared with urinary clearance by iothalamate.5

Wienek et al compared GFR measurement using 125I-iothalamate to determine the performance of CKD-EPI, MDRD and Cockcroft-Gault. It appeared that absolute bias for all the predictive equations was influenced by both gender and age. They also reported that CKD-EPI creatinine gave the best estimation of GFR although its accuracy was close to that of the MDRD.4 Kilbride et al measured GFR in an elderly European population using iohexol clearance and compared it to predictive equations. They concluded that the CKD-EPI creatinine equation appeared to have less bias and was more accurate than the MDRD equation. They also reported that the CKD-EPI creatinine equation is suitable in older people as in younger people of European ancestry.10

In the present study, the other predictive equations underestimated GFR in all patients and in clinical subsets of CKD, transplant, GFR categories, different ages, and BMI groups. This finding has an important implication in that predictive equations other than CKD-EPI might be misinterpreted and increase the risk of a false positive distribution of CKD among the Saudi population. The accuracy of CKD-EPI has an important implication for public health and clinical practice and can even replace other predictive equations for estimation of GFR in Saudi adults. Another study have also reported an underestimation of GFR by MDRD equation.11

Cater et al estimated GFR in an adult UK population and found a higher eGFR by CKD-EPI, particularly among patients 18-59 years old as compared to the MDRD equation.12 Lujan et al reported that the GFR MDRD equation predicted a lower GFR than CKD-EPI creatinine in a comparison of 85 living kidney do-

Table 4. Performance of predictive equations for estimation of GFR in relation to GFR measured by inulin.

| Category               | Mean GFR (SD) | Mean difference | 95% CI for bias | SD of bias for precision | Limits of agreement |
|------------------------|---------------|-----------------|-----------------|--------------------------|---------------------|
| GFR inulin             | 51.54 (33.8)  | -3.2            | -6.02 to 0.32   | 7.71                     | -18.3, 11.92        |
| MDRD                   | 48.35 (33.7)  | -3.2            | -6.02 to 0.32   | 7.71                     | -18.3, 11.92        |
| CKD-EPI-creatinine     | 52.6 (34.4)   | -1.1            | -2.05 to 4.19   | 8.5                      | -15.6, 17.76        |
| Cystatin C             | 41.4 (30)     | -10.2           | -16.4 to 3.89   | 17.1                     | -43.66, 23.35       |
| CKD cystatin creatinine| 45.03 (30.9)  | -6.5            | -10.78 to 2.24  | 11.6                     | -29.33, 16.3        |

Values are ml/min/1.73 m².

Figure 2. eGFR determined by MDRD and GFR measured by inulin clearance.

Figure 3. Bland-Altman plots comparing the GFR calculated by MDRD with the GFR measured by the inulin clearance.
In contrast to our result, the study by Veronese et al of South Brazilian patients showed that CKD–ePi GFR underestimated GFR for GFR >60 and had low accuracy. Their explanation was that the population was of mixed ethnicity with a predominance of Germans, Italians, Portuguese, Spanish, along with native Indians and African blacks. Mixed ethnicity may have uniquely affected creatinine production and the performance of estimated GFR formulas.

In the present study, the CKD-EPI cystatin C and creatinine equation had maximum bias compared with the CKD-EPI and MDRD. This is in agreement with Liu et al who reported that the bias of the CKD-EPI creatinine-cystatin C equation was greater than with other equations. However, they suggested that the CKD-EPI creatinine-cystatin C equation is suitable for an elderly Chinese population.

The present study has shown that the value of GFR in renal transplant patients using the CKD-EPI creatinine equation was more accurate and closer to measured GFR by inulin clearance and had less bias than the other equations. In contrast to our findings, the study of Masson et al and Uwe et al found that the CKD-EPI creatinine equation did not provide a better GFR prediction in renal transplant patients compared with the MDRD study equation even in the earlier CKD stages in Caucasian patients. However, our findings are consistent with the findings of White et al who studied 207 stable kidney transplanted patients using the plasma clearance of (99m)Tc-diethylenetriamine penta-acetic acid and compared to the GFR equation. They showed that CKD-EPI creatinine improved the GFR in renal transplant and that CKD-EPI can replace MDRD.

The present study is the first comprehensive study from the region using inulin clearance to compare with GFR estimated by predictive equations. Furthermore, we have evaluated the performance of different predictive equations in several subsets of clinical conditions like renal transplant, chronic kidney disease, BMI, age, and gender, which were lacking in previous studies from the region. However, the present study had a small sample size and we did not include comorbid diseases like diabetes, HCV, and other co-morbidities as well as old age >80 years.

In conclusion, we conclude that the CKD-EPI creatinine equation is more accurate, precise and less biased in the estimation of GFR in a Saudi population and in all subgroups such as age, stages of CKD and transplant patients. GFR predicted by MDRD was second after CKD-EPI creatinine while other predictive equations such as CKD-EPI cystatin C, and CKD-EPI creatinine-cystatin were inferior to CKD-EPI creatinine and MDRD formula in accuracy and precision.

Acknowledgments

I would like to give special thanks to Dr. Shaffi Ahamed and to Mr. Amir Marzouk for their immense effort and assistance in the statistical analysis of the study.
REFERENCES

1. Levey AS, Atkins R, Coresh J, Cohen EP, Collins AJ, Eckardt KU, et al. Chronic kidney disease as a global public health problem: Approaches and initiatives – a position statement from Kidney Disease: Improving Global Outcomes. Kidney Int. 2007 Aug; 72(3):247-59.

2. Hajhosseiny R, Khavandi K, Goldsmith DJ. Cardiovascular disease in chronic kidney disease: untying the Gordian knot. Int J Clin Pract. 2013 Jan;67(1):14-31

3. Bostom AG, Kronenberg F, Ritz E. Predictive performance of renal function equations for patients with chronic kidney disease and normal serum creatinine levels. J Am Soc Nephrol. 2002 Aug; 13(8):2140-4.

4. Michels WM, Grootendorst DC, Verduijn M, Elliott EG, Dekker PW, Krediet RT. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. Clin J Am Soc Nephrol. 2010 Jun; 5(6):1003-9.

5. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May 5; 150(9):604-12.

6. Jones GR. Use of the CKD-EPI equation for estimation of GFR in an Australian cohort. Pathology. 2010;42(8):487-8.

7. Alsuwaida AQ, Farag YM, Al Sayyari AA, Mousa D, Alhejaili F, Al-Hebri A, et al. Epidemiology of chronic kidney disease in the Kingdom of Saudi Arabia (SEEK-Saudi investigators) - a pilot study. Saudi J Kidney Dis Transpl. 2010 Nov; 21(6):1066-72.

8. National Kidney Foundation. KDQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002 Feb; 39(2 Suppl 1):S1-266.

9. Al Wakeel JS, Hammad D, Al Suwaida A, Tarif N, Chaudhary A, Insani A, et al. Validation of predictive equations for glomerular filtration rate in the Saudi population. Saudi J Kidney Dis Transpl. 2009 Nov; 20(6):1030-7.

10. Kilbride HS, Stevens PE, Eaglestone G, Knight S, Carter JL, Delaney MP, et al. Accuracy of the MDRD (Modification of Diet in Renal Disease) study and CKD-EPI (CKD Epidemiology Collaboration) equations for estimation of GFR in the elderly. Am J Kidney Dis. 2013 Jan; 61(1):57-66.

11. Matsushita K, Mahmoodi BK, Woodward M, Emberson JR, Jafar TH, Jee SH, et al. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. JAMA.2012 May 9; 307(18):1941-51.

12. Carter JL, Stevens PE, Irving JE, Lamb EJ. Estimating glomerular filtration rate: comparison of the CKD-EPI and MDRD equations in a large UK cohort with particular emphasis on the effect of age. CJM.2011 Oct;104(10):839-47.

13. Lujan PR, Chuichiu C, Douthat W, de Arteaga J, de la Fuente J, Capra RH, et al. CKD-EPI instead of MDRD for candidates to kidney donation. Transplantation.2012 Sep 27;94(6):637-41.

14. Veronese FV, Gomes EC, Chanan J, Carraro MA, Camargo EG, Soares AA, et al. Performance of CKD-EPI equation to estimate glomerular filtration rate as compared to MDRD equation in South Brazilian individuals in each stage of renal function. Clin Chem Lab Med. 2014 Dec; 52(12):1747-54.

15. Liu X, Xu H, Zheng Z, Wang C, Cheng C, Shi C, et al. Estimating glomerular filtration rates in elderly Chinese patients with chronic kidney disease: performance of six modified formulae developed in Asian populations.Clin Interv Aging. 2013;8:899-904.

16. Masson I, Flament M, Maillard N, Rule AD, Vrtovecnik F, Peraldi MN, et al. MDRD versus CKD-EPI equation to estimate glomerular filtration rate in kidney transplant recipients. Transplantation. 2013 May 27; 95(10):1211-7.

17. Pöge U, Gerhardt T, Stoffel-Wagner B, Sauerbruch T, Woitas RP. Validation of the CKD-EPI formula in patients after renal transplantation. Nephrol Dial Transplant. 2011 Dec; 26(12):4104-8.

18. White CA, Alkari A, Doucette S, Ferguson D, Knoll GA. Estimating glomerular filtration rate in kidney transplantation: is the new chronic kidney disease epidemiology collaboration equation any better? Clin Chem. 2010 Mar; 56(3):474-7.