Validation of the CKD-EPI formula in patients after renal transplantation

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Abstract

Background. Accurate calculation of glomerular filtration rate (GFR) is crucial in the management of patients after kidney transplantation (KTx). Recently, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was introduced to estimate GFR in chronic kidney disease patients. However, to date the diagnostic value of this equation remains to be determined in patients after KTx.

Methods. We analysed the CKD-EPI formula in comparison to the re-expressed Modification of Diet in Renal Disease (MDRD) equation in 170 stable patients after renal transplantation. Correlation, bias, precision and accuracy within 30 and 50% of true GFR were determined. GFR was measured by technetium-diethylenetriamine pentaacetic acid clearance [39.6, 95% confidence interval (CI): 37.3–42.0 mL/min/1.73m²].

Results. The results for the MDRD and CKD-EPI equations correlated well with GFR (0.82; 0.83, respectively). GFR calculated by MDRD (44.1, 95% CI: 41.6–46.8 mL/min/1.73m²) and CKD-EPI (47.7, 95% CI: 44.7–50.7 mL/min/1.73m²) overestimated true GFR significantly (P < 0.001). Precision was not significantly different between MDRD and CKD-EPI (10.9 versus 10.0 mL/min/1.73m², respectively). Accuracy within 30% of true GFR was significantly higher for MDRD (71.8%) than for CKD-EPI (64.1%, P = 0.0014). Accuracy within 50% of true GFR did not differ significantly (MDRD: 89.4% versus CKD-EPI: 84.7%, P = 0.06).

Conclusion. The new CKD-EPI formula did not improve the estimation of GFR in Caucasian patients after renal transplantation in this study.

Keywords: CKD-EPI formula; diagnostic accuracy; glomerular filtration rate; kidney transplantation; precision

Introduction

Levey et al. [1] recently proposed a new equation for calculating the glomerular filtration rate (GFR) to resolve disadvantages of the Modification of Diet in Renal Disease (MDRD) formula. The so-called Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is based on pooled data of 8254 participants from 10 studies and validated in a cohort of 3896 participants from additional 16 studies. It could be demonstrated that the CKD-EPI equation was superior to the MDRD formula with respect to bias, precision and accuracy in participants with GFR >60 mL/min/1.73m² and as accurate as the MDRD equation in the subgroup of patients with GFR <60 mL/min [1].

In patients after kidney transplantation (KTx), precise calculation of GFR is important for management and follow-up. The MDRD formula has been found to perform reasonably well in these patients but was far from being an ideal estimation formula [2]. Thus, we questioned whether the new CKD-EPI equation may be superior to the MDRD equation and whether it may offer advantages for the GFR calculation in patients after KTx.

Materials and methods

A total of 170 consecutive post-transplant patients [169 Caucasian, 68 female, 102 male; age: 48.9, 95% confidence interval (CI): 47.0–50.9 years, body mass index: 24.9, 95% CI: 24.3–25.6 kg/m²] participated in the study. The inclusion criterion of this study was stable renal function which was defined as a variability of creatinine <15% within 2 weeks of GFR measurement. Exclusion criteria were instable renal function, systemic or overt urinary tract infection and intake of medication affecting tubular secretion of creatinine (e.g. sulfamethoxazole/trimethoprim, cimetidine).

The cohort included 16 post simultaneous kidney and pancreas transplant patients and 3 post combined liver and KTx patients.

This prospective study was approved by the local Ethics Committee and written informed consent was obtained from all patients enrolled in the study.

Immunosuppressive regimen consisted of cyclosporine A in 90 and tacrolimus in 62 patients. Seventeen patients were on sirolimus-based immunosuppression. Calcineurin inhibitor treatment was combined with mycophenolate-mofetil in 87 patients and with azathioprine in 5 patients. All but four participants received corticosteroids. Mean corticosteroid dosage was 5.8 mg/day.

GFR was determined as technetium-diethylenetriamine pentaacetic acid (¹⁹⁵Tc-DTPA) clearance with a single injection technique with a two-point sampling approach at 1 and 3 h post-injection according to the method described by Russell et al. [3]. The patients underwent ¹⁹⁵Tc-DTPA clearance determinations covering a wide range of renal function (creatinine 1.77, 95% CI: 1.65–1.89 mg/dL, range: 0.76–6.36 mg/dL) and time since transplantation (71.2, 95% CI: 60.3–82.1, range: 3–278 months).
A blood sample for creatinine measurement was taken in the morning directly prior to the DTPA clearance. Creatinine was determined on a Dimension RxL™ clinical chemistry analyser (Dade Behring, Marburg, Germany) with an assay based on a modification of the kinetic Jaffe reaction. The creatinine assay was adjusted for calibration with the isotope dilution mass spectrometry (IDMS) method as reported elsewhere [4]. The assay range is 0–20 mg/dL (0–1768 μmol/L). The intra-assay coefficient of variation (CV) was 0.03 [mean: 0.85 mg/dL (75 μmol/L), n = 20], while the interassay CV was 0.05 [mean: 0.85 mg/dL (75 μmol/L), n = 20].

The GFR was calculated by using the re-expressed MDRD [5] and the CKD-EPI [1] equations.

Statistics

Data are given as mean with a 95% CIs for the mean unless indicated otherwise. P-values <0.05 were considered significant. Pearson’s correlation coefficients were calculated between DTPA clearance and estimates of GFR by a linear correlation analysis. Comparison of the correlation coefficients was performed using Z-statistics. The mean difference between equation-based GFR and the measured GFR (99mTc-DTPA clearance) was used to determine the bias. Pairwise comparison of the mean difference was performed using paired t-test. The precision of the estimated was determined as SD of the mean difference between measured GFR (mGFR) and estimated GFR (eGFR) [6]. Accuracy integrating precision and bias was calculated as the percentage of GFR estimates within 10, 30 and 50% deviation of the true GFR as suggested [7]. McNemar test was used to evaluate the degree of accuracy [8]. Moreover, a graphical approach to assess accuracy was carried out according to Bland and Altman [9]. Analyses were performed using StatView™ (version 5.0 for Windows; SAS Institute Inc. Cary, NC). Bland and Altman analyses of the true and estimated GFR were performed with MedcalcTM Software, Mariakerke, Belgium.

Results

Mean measured GFR was 39.6 (37.3–42.0) mL/min/1.73m² in our cohort. The calculated GFR of the CKD-EPI- and the MDRD-formulae were 47.7 (44.7–50.7) and 44.1 (41.4–46.8) mL/min/1.73m², respectively. Thus, calculated GFR of the CKD-EPI- and the MDRD-formulae differed significantly from true GFR (P < 0.0001 for both). Additionally, the results of the CKD-EPI- and the MDRD-formulae differed significantly from one another (P < 0.0001).

The regression coefficients of the CKD-EPI- and the MDRD-formulae with the GFR were similar and did not differ significantly (Table 1). Bias of the MDRD equation (4.49 mL/min/1.73m²) was significantly smaller than for the CKD-EPI formula (8.07 mL/min/1.73m²; P < 0.001). Consequently, relative bias was found to be lower for the MDRD formula than for the CKD-EPI equation (MDRD: 11.9% and CKD-EPI 20.2%). The precisions of the CKD-EPI- and the MDRD-formulae showed no differences (10.9 and 10.0 mL/min/1.73m²; P = 0.150).

The accuracy of the CKD-EPI formula within 10, 30 and 50% of true GFR (25.9, 64.1 and 84.7%) was lower than the accuracy of the MDRD equation (31.2, 71.8 and 89.4%). The difference for the 30% accuracy reached the level of significance (P = 0.0014, McNemar test), whereas the 10 and 50% accuracy did not (P = 0.17 and P = 0.06, respectively).

For a more detailed analysis, the patients were divided into two groups according to the results from the DTPA clearance: GFR < 60 mL/min/1.73m² or >60 mL/min/1.73m². The results are presented in Table 2.

In both subgroups, bias of the MDRD formula was significantly lower than that of the CKD-EPI equation. Precision was similar in the mGFR > 60 mL/min/1.73m² subgroup. In the subgroup, mGFR < 60 mL/min/1.73m² precision was somewhat better for the MDRD group (P = 0.04).

In KTx patients with mGFR >60 mL/min/1.73m², both equations showed a trend to a lower bias than in the mGFR < 60 mL/min/1.73m² subgroup. Conversely, precisions of both equations were significantly lower in the patients with GFR >60 mL/min/1.73m². Consequently, overall the values for accuracy were similar in both subgroups.

Bland and Altman plots

The differences between calculated and measured values of GFR were illustrated using a graphical technique according to Bland and Altman (Figure 1). These figures display the span between +1.96 and –1.96 SD of the mean difference (limits of agreement), which represents the 95% CI. A somewhat smaller limit of agreement was found for the MDRD formula (39.4 mL/min/1.73m²) in comparison to the CKD-EPI formula (42.7 mL/min/1.73m²).

Discussion

In this study, we assessed the diagnostic performance of the recently proposed new CKD-EPI formula to determine GFR in patients after KTx. Our results showed no improvement in all tested analyses in comparison to the MDRD formula.

The development of the MDRD formula based on the data of patients with chronic kidney disease (CKD) and a GFR <60 mL/min/1.73m². It has been found that the MDRD formula showed a reliable performance in estimating GFR in CKD patients. In patients after RTx, the MDRD equation has been found to be superior to the Cockcroft Gault formula [10–12]. However, those studies which investigated the performance of the MDRD equation to predict GFR in KTx patients were not conclusive. A systematic review of the available data reported a wide range of accuracy and bias [13]. Accordingly, one study found an underestimation by 10 mL/min/1.73m² in 117 KTx patients, whereas others reported an overestimation of 6.5 mL/min/1.73m² [10, 14]. Thus, discrepancies in (un)reported patients characteristics, divergences in creatinine determination and calibration and differences in the GFR measurement may have accounted for the heterogeneity of the study results [13]. Thus, the MDRD formula should be used with some caution in patients after KTx. Moreover, interest arises whether the CKD-EPI equation is recommendable as an appropriate substitute.

As a consequence of the development process of the MDRD formula, this equation underestimates GFR in patients or volunteers with higher GFR values. Thus, the CKD-EPI estimation was conducted to omit this underestimation. Consequently, the data set of the CKD-EPI
formula included many participants with normal or only slightly reduced GFR resulting in a mean GFR of 68 mL/min/1.73m² in the development and the validation cohort. The validation process of the CKD-EPI formula showed an improved performance if mGFR is >60 mL/min/1.73m² and a similar performance in patients with mGFR <60 mL/min/1.73m² in comparison to the MDRD formula. 

External validation of the CKD-EPI equation found comparable results for the CKD-EPI and MDRD equations [15–17]. There were trends to overestimate mGFR in patients with lower true GFR and to underestimate in patients or volunteers with normal GFR [15]. On the contrary, Stevens [18] found a higher accuracy by using the CKD-EPI equation.

Two manuscripts were published regarding the value of the CKD-EPI equation in KTx. One study reported a significant lower bias of −4.5 mL/min/1.73m² for the CKD-EPI equation in comparison to the re-expressed MDRD formula (−8.0 mL/min/1.73m²) [19]. No differences were found with respect to precision or accuracy in the overall cohort.

In contrast, a second study found a considerable overestimation of mGFR by the MDRD and the CKD-EPI equation in a steroid free cohort at 1 year after engraftment (2.4 versus 6.9 mL/min/1.73m², respectively) [20]. Similar results were observed in the (smaller) steroid maintenance study cohort (3.7 versus 9.5 mL/min/1.73m²). The CKD-EPI equation tended to lower precision, although the significance of the difference had not been determined.

Recently, a study from the Mayo Clinic Rochester, MN (so far published in abstract form only) found a bias of 1% by the MDRD equation in contrast to a bias of 8% for the CKD-EPI formula in 1375 KTx patients (Renal Week 2010, TH-FC084) [21]. In our present study, the CKD-EPI was found to be inferior to the MDRD equation with respect to bias and accuracy within 30%, whereas no significant differences were found for precision and accuracy within 10 and 50%.

A subgroup analysis of our patients showed a trend to lower bias but a significant inferior precision for both equations when mGFR exceeded 60 mL/min/1.73m². Unfortunately, this subgroup comprised only 20 patients. In comparison to the study of Kukla [20], we found similar results for both equations with respect to bias and accuracy. However, precision was lower in the Kukla study. Similar to our results, the study from the Mayo Clinic found a higher bias of the CKD-EPI formula than for the MDRD equation [21]. Nevertheless, the reported relative bias was much lower for both equations than in our study.

White et al. [19] reported an underestimation of mGFR by both equations, even when the results of patients with

| Table 1. Correlation, difference to true GFR, accuracy and precision of GFR estimates |
|-------------------------------------|-----------------|---------|-------|-----------------|-----------------|-------------------|-------------------|-------------------|
|                                    | Mean GFR        | Range   | r     | P-value       | Mean difference | Median            | SD of mean bias    |
|                                    | (mL/min/1.73m²) |         |       |               | (mL/min/1.73m²) |                   |                   |
| GFR                                | 39.6            | 11.8–82.9 | 0.828 | <0.0001       | +4.49           | +4.13             | 10.0              |
| Re-expressed MDRD                  | 44.1            | 9.2–103  | 0.828 | <0.0001       | +8.07           | +7.41             | 10.9              |
| CKD-EPI                            | 47.7            | 9.3–104  | 0.837 | <0.0001       |                 |                   |                   |

| Table 2. Bias, precision and accuracy of GFR estimates within two subgroups |
|-------------------------------------|-----------------|---------|-------|-----------------|-----------------|-------------------|-------------------|
|                                    | MDRD            | CKD-EPI |
| mGFR > 60                          | n = 20          |         |
| Mean mGFR                          |                 |         |
| Accuracy within 10%                |                 |         |
| n = 150                            |                 |         |
| Mean mGFR                          |                 |         |
| Accuracy within 10%                |                 |         |
| mGFR < 60                          | n = 150         |         |
| Mean mGFR                          |                 |         |
| Accuracy within 10%                |                 |         |

*MDRD, mean difference Group 1 versus Group 2: P = 0.12; CKD-EPI, mean difference Group 1 versus Group 2: P = 0.64; MDRD, SD of mean difference Group 1 versus Group 2: P < 0.001; CKD-EPI, SD of mean difference Group 1 versus Group 2: P = 0.003. *P = 0.0001 versus CKD-EPI; **P = 0.38 versus CKD-EPI; *P = 0.0001 versus CKD-EPI; ***P = 0.04 versus CKD-EPI.
GFR <60 mL/min/1.73m² were compared only. It should be pointed out that the subgroup GFR < 60 mL/min/1.73m² of the White study comprised a similar number of patients as our subgroup. However, the CKD stages were somewhat different within this subgroup with a trend to lower mGFR values in our subgroup (White: CKD3: 81.7%, CKD4: 14.7%, CKD5: 3.7% versus CKD3: 65.3%, CKD4: 34%, CKD5: 0.7% in the presented study). Thus, differences in the study cohort may contribute to the different results. Nevertheless, some results are similar: precision data were very similar in both studies. Moreover, the lower negative bias of the CKD-EPI equation represents higher eGFR values calculated from the CKD-EPI equation than from the MDRD formula. In detail, in the subgroup GFR < 60 mL/min/1.73m², the difference between the median bias of the MDRD and the CKD-EPI equation was 10%.

Fig. 1. (A-B) Bland and Altman analysis of GFR estimates. In this analysis, the differences between two methods are plotted against the average of true and estimated GFR for each individual patient. The CKD-EPI formula and the GFR are plotted in figure 1A and MDRD and GFR in figure 1B. Data are given in mL/min/1.73m².
equation was 1.9 mL/min/1.73m² in the study of White and 3.05 mL/min/1.73m² in our study. The results in the subgroup GFR > 60 mL/min/1.73m² were 5.8 and 7.0 mL/min/1.73m², respectively. Thus, all mentioned studies showed higher eGFR values for the recently developed CKD-EPI equation in patients after KTx.

Stevens et al. [22] reported data from a large cohort of patients with prior organ transplantation that included a considerable number of patients after KTx. Similar to White’s findings, an underestimation of the mGFR was seen for both equations. Additionally, the bias was smaller for the CKD-EPI formula.

The differences between our results and studies mentioned above may be related to several factors. First, our cohort of patients after renal transplantation had a mean mGFR of 39.6 mL/min/1.73m² which is considerably lower than in the most other studies. Thus, the advantage of the CKD-EPI equation reported at higher GFR levels could not be transferred to our low GFR values in patients after KTx.

Second, it should be stressed that we used a DTPA clearance to determine GFR, whereas the development cohort of the CKD-EPI formula comprised ten different studies using iothalamate to determine GFR. Since some inaccuracy between these exogenous filtration markers are known, the technique of GFR determination may also contribute to our findings [23, 24].

Third, despite IDMS standardization of creatinine determination differences between laboratories involved in the studies mentioned above and our laboratory cannot be excluded and may contribute to the different findings of the eGFR values.

Fourth, our cohort comprised virtually only of Caucasians and may not be comparable to other ethnic groups.

Finally, our study cohort is relatively small in comparison to the large cohort of patients in the CKD-EPI analysis. Thus, our results may not be transferable to a larger and more heterogeneous population of kidney transplant recipients.

In conclusion, the validation of the recently introduced CKD-EPI formula in our cohort of patients after KTx found a considerable overestimation of GFR and seems not to improve the GFR estimation in comparison to the re-expressed MDRD equation. Keeping the different study results in mind the value of the CKD-EPI equation in KTx patients needs further validation, especially when GFR is estimated <60 mL/min/1.73m².

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