Performance of estimated glomerular filtration rates to monitor change in renal function in kidney transplant recipients

Jean-Pierre Fauvel1, Aoumer Hadj-Aissa2, Fanny Buron3, Emmanuel Morelon3 and Michel Ducher1

1Département de Néphrologie et Hypertension, Hospices Civils de Lyon, Hôpital Edouard Herriot, Lyon, France, 2Laboratoire d’explorations fonctionnelles rénales et métaboliques, Hospices Civils de Lyon, Hôpital Edouard Herriot, Lyon, France and 3Département de Transplantation et Immunologie clinique, Hospices Civils de Lyon, Hôpital Edouard Herriot, Lyon, France

Correspondence and offprint requests to: Jean-Pierre Fauvel; Email: jean-pierre.fauvel@chu-lyon.fr

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ABSTRACT

Background. Glomerular filtration rate estimates (e-GFR) are often used to evaluate the changes in renal function, but have not been validated for this purpose in kidney transplant recipients (KTRs). The aim of this study was to evaluate the validity of e-GFR for monitoring serial changes in renal function in KTR using directly measured GFR by inulin clearance (I-GFR) as the reference standard.

Methods. Performances of inverse serum creatinine (1/creat) and Cockcroft and Gault, Modification of Diet in Renal Disease, and Chronic Kidney Disease Epidemiology Collaboration formulas were assessed to estimate the changes in I-GFR.

Results. A total of 1935 I-GFR clearance procedures were performed in 631 KTRs who underwent serial measurements between 2003 and 2009. The baseline median I-GFR were 51.0 mL/min/1.73 m² (confidence interval 95%: 23–84 mL/min/1.73 m²]. The performances of 1/creat and formulas for detecting the I-GFR variations between two consecutive measurements (n = 1304) were similar. To detect the variations of <20% (increase or decrease), sensitivities ranged between 50 and 56%, and specificities between 64 and 69%. To detect the variations >20% (increase or decrease), sensitivities ranged between 27% and 39%, and specificities between 88 and 97%. Bland-Altman plots confirmed the scattering of values for individual patients.

Conclusions. In a population of Caucasian KTRs, the mean changes in GFR are correctly estimated whatever the formula used in the range of 23–84 mL/min/1.73 m² and can thus be applied in population studies. However, in clinical practice, individual changes in GFR evaluated by formulas should be interpreted with caution in KTRs.

INTRODUCTION

The management of kidney transplant recipients (KTRs) requires the accurate estimates of glomerular filtration rate (GFR), the primary indicator of graft function [1, 2]. The change in GFR is the most reliable indicator of long-term graft survival [3, 4] and is one of the principal criteria used in clinical research studies on transplantation.

Changes in renal function in clinical studies use the reciprocal of serum creatinine (1/creat) and Cockcroft and Gault, Modification of Diet in Renal Disease, and Chronic Kidney Disease Epidemiology Collaboration formulas to estimate the changes in GFR. The formula derived from the Modification of Diet in Renal Disease (MDRD) study was developed from the data of patients with renal failure to estimate GFR [5]. The Cockcroft and Gault (CG) formula was developed to predict creatinine clearance [6]. The formula proposed by the ‘Chronic Kidney Disease Epidemiology Collaboration’ formula (CKD-EPI) was proposed to overcome the lack of precision of the preceding formulas and their poor performance in the event of high GFR [8].

GFR estimates were developed originally to assess the baseline renal function and identify patients with chronic kidney disease (CKD). Although GFR estimates were used to evaluate...
serial changes in renal function, they have not been validated for this purpose in KTR.

Accordingly, the aim of this study was to evaluate the validity of GFR estimates for assessing serial changes in renal function in KTR using directly measured GFR by inulin clearance (I-GFR) as the reference standard.

**Materials and Methods**

The performance of 1/creatinine and of the formulas to estimate the changes in GFR was assessed in all of the 631 KTRs who had at least two serial inulin clearance values between February 2003 and March 2009 at the Edouard Herriot hospital in Lyon (France). Inulin clearance (I-GFR) values were always measured at a stable state. Trimethoprim for anti-pneumocystis prophylaxis was stopped 6 months after transplantation. Steroid dosage was tapered off to 5 mg per day during the first 3 months after transplantation and then steroids were continued at this dosage. In this retrospective study, the procedure followed is in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

**Measurement of GFR**

I-GFR was measured by the gold standard method, i.e. urinary inulin clearance [9]. Briefly, inulin clearance was measured in the morning after fasting. Two peripheral venous catheters were inserted, one in each arm, one for inulin infusion and one for blood sampling. The inulin infusion (Inutest®, Frésénius Kabi, Graz, Austria) was started as a 0.03 g/kg loading dose over 12 min and was then continued at a constant rate of 0.33 mg/kg/min throughout the procedure. At the beginning, the patient was asked to empty the bladder and a first blood sample was taken for serum creatinine assay. At 45 min, the bladder was emptied again. This was followed by three consecutive 30-min periods with blood sampling (for inulin assay) in the middle of each period and a urine collection (volume, inulin assay) at the end. Where necessary, periods were added and/or urinary catheterization performed, depending on the urine output and voiding disorders. Inulin clearance was calculated separately for each period (urine excretion rate over plasma concentration). The results were expressed as the mean of three to five clearances. Inulin was

| Table 1: Population characteristics and distribution at the time of the first GFR measurement |
|-----------------------------------------------|----------|----------|
| **Mean ± SD**                                 | **Number** | **Percentage** |
| Total                                         | 631      | 100      |
| Gender                                        |          |          |
| Men                                           | 406      | 64       |
| Women                                         | 225      | 36       |
| Age (years)                                   | 50 ± 13  |          |
| ≤40                                           | 159      | 25       |
| 40 < age ≤60                                  | 323      | 51       |
| >60                                           | 149      | 24       |
| BMI (kg/m²)                                   | 24.1 ± 4.1 |          |
| <18.5                                         | 26       | 4        |
| 18.5 ≤ BMI < 25                               | 359      | 57       |
| 25 ≤ BMI < 30                                 | 204      | 32       |
| ≥30                                           | 42       | 7        |
| I-GFR (mL/min/1.73 m²)                        | 54 ± 18  |          |
| GFR <30                                       | 44       | 7        |
| 30 ≤ GFR <60                                  | 335      | 53       |
| 60 ≤ GFR                                      | 252      | 40       |
| Creatinine (µmol)                             | 129 ± 41 | 631      | 100     |
| e-GFR CG (mL/min/1.73 m²)                     | 58 ± 18  | 631      | 100     |
| e-GFR MDRD (mL/min/1.73 m²)                   | 52 ± 17  | 631      | 100     |
| e-GFR CKD-EPI (mL/min/1.73 m²)                | 56 ± 19  | 631      | 100     |
assayed using an enzymatic colourimetric technique with a Molecular Devices Versamax® microplate reader. The distribution of the baseline I-GFR followed a normal distribution. The baseline median I-GFR was 51.0 mL/min/1.73 m² [95% confidence interval (CI): 23–84 mL/min/1.73 m²].

**Measurement of serum creatinine concentrations**

Sampling was performed before inulin infusion. The method used was a kinetic colourimetric-compensated Jaffé assay. The results for serum creatinine were standardized by linear regression adjustment of the concentrations obtained by the compensated Jaffé assay and the concentrations obtained by liquid chromatography-mass spectrometry (LCMS). The complete methodology to measure and standardize creatinine values has already been published [10].

**Estimation of GFR**

GFR was estimated using the CG formula [6], the simplified standardized MDRD formula [7] and the CKD-EPI formula [8]. All of the e-GFRs were normalized by BSA and expressed in mL/min/1.73 m². Standardized creatinine values were used for all the calculations.

**Statistical analysis**

The results of the descriptive analysis were expressed as the mean ± standard deviation for quantitative variables and as percentage for qualitative variables. Normality of the distribution of baseline I-GFR was checked using the Kolmogorov–Smirnov test. Correlation plots illustrated the disagreement between per cent changes in I-GFR, and e-GFR and 1/creat, respectively. Statistical analysis was performed using MedCalc Software version 11 5.1 (MedCalc® Software, Mariakerke, Belgium).

Sensitivity, specificity, PPV and NPV were computed using the usual definitions. Sensitivity, specificity, PPV and NPV were compared using the χ² test with 1 degree of freedom. P < 0.05 was considered as significant.

**RESULTS**

**Performance of 1/creatinine ratio and formulas**

A total of 1935 inulin clearance procedures were performed in the 631 KTRs who underwent serial I-GFR measurements in Lyon between February 2003 and March 2009. Among the 631 included patients, 295, 138, 87, 85, 24 and 2 patients had 2, 3, 4, 5, 6 and 7 I-GFR measurements, respectively. A total of 1304 changes were computed between two consecutive measurements of I-GFR and e-GFR or 1/creat. The mean time elapsed between two consecutive I-GFR measurements was 17.6 ± 11.7 months. A total of 92% of the patients were Caucasian. The mean body weight variation between two consecutive I-GFR measurements was −0.6% ± 6.5. The main characteristics of patients are given in Table 1.

Sensitivity, specificity, PPV and NPV were given in Table 2. The performance of 1/creat and formulas for detecting I-GFR variations were similar. To detect variations of <20% (increase or decrease), sensitivities ranged between 50 and 56% and specificities between 64 and 69%. Positive predicted values (PPVs) ranged between 44 and 50% and negative predicted values (NPVs) between 70 and 74%. To detect variations >20% (increase or decrease), sensitivities ranged between 27 and 39% and specificities between 88 and 97%. PPV ranged between 28 and 64% and NPV between 86 and 92%. Bland–Altman plots of individual data of means of changes versus differences in changes are represented in Figure 1.

**DISCUSSION**

Periodic accurate assessment of changes in renal function is crucial for monitoring the renal function of KTR [2]. Our results show that all of the estimators of changes in renal
function usually used have similar performances. However, they all poorly detect a 20% variation in renal function. We have recently published that the estimates of mean I-GFR were different between formulas, MDRD being the most accurate in this population of KTRs [10]. In most patients differences between eGFR and I-GFR are not large and likely to be not clinically relevant. Thus, to follow-up the mean GFR of a group of KTRs, the MDRD formula used to estimate GFR was accurate. However, for individual monitoring of GFR, none of the estimators was reliable. Reliability of a test is usually assessed by AUC of the ROC curve, sensitivity, specificity, PPV and NPV. Sensitivities were low (around 55%) to detect variations (increase or decrease) in I-GFR of <20%. Surprisingly, sensitivities were even lower (around 33%) to detect higher variations. Specificities were higher (around 65%) to detect variations of <20% but were higher (around 95%) for higher variations. Such results demonstrate that none of the estimators reached a satisfactory level of reliability to be used in clinical practice. Any variation in GFR >20% should be detected by estimators since it is of clinical relevance. For a pragmatic approach, PPV and NPV are more suitable to check the ability of tests to establish a diagnosis [11]. PPV and NPV did not reach a satisfactory level of prediction to be usable in clinical practice. Calculations of sensitivities, specificities, PPV and NPV are biased by a ‘threshold effect’. Bland-Altman plots showed the scattering of values for individual patients. The regression trends showed that, in the whole population, estimation of changes in I-GFR were correctly estimated with a significant trend with 1/creat and the CG formula. However, for individual patients, the standard deviation that estimated the scattering of values confirmed the poor predictive value of formulas when estimating individual changes in GFR. Our results, implemented in a larger population, with a longer follow-up, using an IDMS-traceable creatinine, and inulin clearances as gold standard, are in agreement with previous studies [12, 13]. Using eGFR for assessing changes in KTR may be misleading clinically and may lead to delayed (i) diagnosis of renal allograft pathology and (ii) appropriate management of progressive CKD. Furthermore, using 1/creat or formulas to estimate modifications in renal function in KTRs during clinical trials remains questionable. The variability in the estimation of changes should at least be taken into account when computing the number of subjects to include in clinical trials. It is not surprising that all the estimators had similar performances.

**FIGURE 1:** Bland–Altman plots of per cent variations between two consecutive determinations in I-GFR and per cent variations in 1/creat (A), and eGFR calculated by CG (B), MDRD (C) and CKD-EPI (D) formulas. Horizontal lines are mean bias with 95% CI of the bias. The regression line is also shown with its 95% CI.
Indeed, all the indices are calculated from the inverse of creatinine values. When considering intra-individual variations, the change in creatinine is the major determinant. In our study, the change in age has little weight since the mean interval between GFR measurements was 17 months. The change in weight influenced only CG estimation of GFR. In our study, GRF was measured under stable conditions and changes in weight were negligible. Certain features of KTRs can alter the validity of these formulas: marked variation in muscle mass during treatment management due to corticosteroids, increased catabolism caused by opportunistic infections and the effect of drugs such as trimethoprim on the tubular secretion of creatinine. In our study, these parameters had little influence since I-GFR was measured under stable clinical conditions. Thus, body weight varied little between measurements, none of the subjects took trimethoprim and the mean steroid dosage was 5 mg per day during the study period. This can also be considered as a limitation of our study and our results cannot be applied to detect a variation in GFR in the event of acute kidney transplant rejection. It is important to note that most of our patients were Caucasian (92%), which limits its application in black patients. However, the strengths of our study lie in the fact that the baseline I-GFR range was broad [median I-GFR: 51 mL/min/1.73 m²; 95% CI (23–84 mL/min/1.73 m²)] in a large patient cohort, we used inulin clearance as the gold standard for measuring GFR and we used a standardized LCMS serum creatinine assay method.

To conclude, in a population of largely Caucasian KTRs, changes in I-GFR are poorly estimated by formulas implemented to assess GFR. The mean changes in GFR are correctly estimated whatever the formula used in the range of 23–84 mL/min/1.73 m² and thus can be applied in population studies. However, in clinical practice, individual changes in GFR evaluated by formulas should be interpreted with caution in KTRs.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest.