Assessment of the Renal Function in Potential Donors of Living Kidney Transplants: Expanded Study

L.B. Macías[a,*], M.S. Poblet[a], N.N. Pérez[a], R.I. Jerez[b], F.M. Gonzalez Roncero[a], G.B. Blanco[a], M.A.P. Valdivia[a], A.S. Benjumea[a], and M.A. Gentil Govantes[a]

[a]UGC-Nefrourológica and [b]y Medicina Nuclear, Hospital Virgen del Rocío, Sevilla, SpainF.M. Gonzalez Roncero

ABSTRACT

Introduction. It is very important to determine as accurately as possible the renal function in potential living renal transplant donors, especially those with limited renal function (CrCl <90 mL/m/1.73 m^2), age older than 50 years, and cardiovascular risk factors that might favor the development of long-term kidney diseases.

Objective. The objective of this study was to compare the direct measurement of glomerular filtration rate (GFR) using EDTA-Cr51 and the estimations based on creatinine (eGFR): Cr clearance (CCr) with 24-hour urine and estimated using Cockroft-Gault (adjusted by using body surface area–Mosteller formula-SC), MDRD-4, MDRD-6, and CKD-EPI to determine the usefulness of different methods from EDTA-Cr51to evaluate the kidney function.

Patients and Methods. The kidney function evaluation has been made to 105 potential kidney donors using the EDTA-Cr51 method. The GFR obtained through the EDTA-Cr51 is compared with the CCr values in 24-hour urine and eGFR based on creatinine (Cockcroft-Gault, MDRD4, MDRD6, and CKD-EPI).

Results. Using the Bland Altman graphic we have observed that the most dispersed results are obtained with the eGFR using CCr in 24-hour urine and CKD-EPI. By means of Pasing & Bablock, we realized that MDRD-4 and MDRD-6 show the highest approximation to the reference method proposed to be substituted, whereas CCr shows a high dispersion.

Conclusions. eGFR using MDRD-4 and MDRD-6 formulas reveal the best adjustment to the measure by EDTA-Cr51. This might represent the best option if a direct eGFR measure is not available.

THE CURRENT optimal treatment of end-stage renal failure is kidney transplantation, but this therapy is limited by the shortage of deceased donors and the comorbidity of the patients suffering from kidney failure, which hinder the transplant. The living donor kidney transplantation allows eliminating the lack of organs of deceased donors and additionally shows better results than the cadaver transplantation [1,2].

Nowadays the living donation age is increasing [3,4] as well as its cardiovascular risk factors, so a more accurate estimation of the renal function is required to avoid long-term development of nephropathy.

The mGFR through nonisotopic external markers (inulin, ioexol, iothalamate) or isotopic techniques (125I iothalamate, EDTA-Cr51, 99Tc DTPA) has been considered the "gold standard" for the kidney failure evaluation. Nonetheless, these are not available in many medical centers due to the complexity of the technique. The eGFR with 24-hour urinary creatinine clearance is frequently used because of its availability; however, it is laborious and frequently mistaken.

The eGFR using serum-based creatinine formulas (Cockroft-Gault, aMDRD, and CKD-EPI) are not validated for this specific population, because these come from a population

*Address correspondence to Lourdes Ballestero Macías, University Hospital Virgen del Rocio, Avenue Manuel Siurot sn, 41013, Seville, Spain. E-mail: lobama85@hotmail.com

360 Park Avenue South, New York, NY 10010-1710

0041-1345/15
http://dx.doi.org/10.1016/j.transproceed.2015.09.029

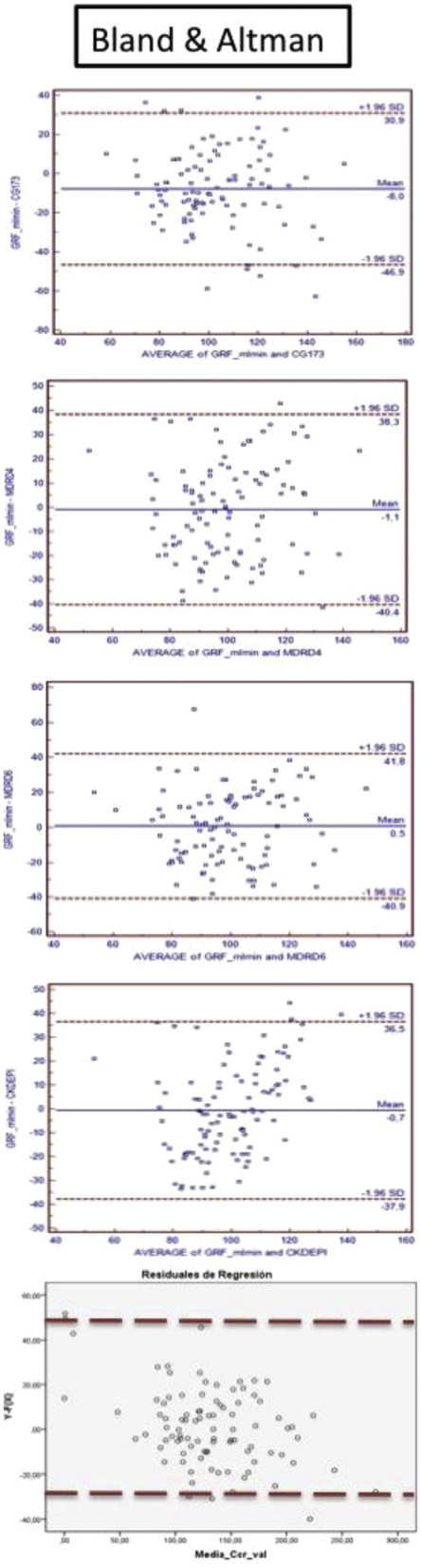


Fig 1. Through the Bland-Altman graphic we observe dispersed values of the generalized form by the different formulas showing extreme values, out from the 1.96 standard deviation (SD), in CCr and CKD-EPI. In the rest of the formulas, although values are dispersed, they are within 1.96 SD or close to it.

with a lower rate of glomerular filtration [5–9]. One of the main limitations of the eGFR using MDRD is its low correlation with the real GF for values > 60 mL/min/1.73 m^2. Nonetheless, it has been communicated that the average CCr and MDRD give a good approximation to the mGFR with 125 iothalamate [10]. Levey et al, from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI group) of the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK), creator of the MDRD equation, has recently published a new equation, the CKD-EPI, which is more accurate and has been validated with the American population [12]. This equation aims to achieve a better performance in the normal and higher ranges of FG. Nevertheless, the accuracy of this equation in living donors, especially in older people, has not been proven.

Due to the complexity of the direct measure of GF and that not all centers have a validated technique, we have realized a comparative study between the mGFR with EDTA-Cr51 in respect to the measure of endogenous creatinine and the eGFR by means of serum creatinine–based formulas.

MATERIALS AND METHODS

We have evaluated 105 potential living kidney donors from April 2011 to December 2014 in the Virgen del Rocio University Hospital. The mGFR has been done by the clearance of Cr-51-EDTA and the eGFR by CCr in 24-hour urine and serum creatinine–based formulas before donation as part of the screening program.

GFR Measured

Based on the recommendations made by the British Society of Nuclear Medicine [17] to the calculation of the GF, we applied the second exponential method, according to Mistry [18], with Chantler et al's [19] correction. GFR = [VD × 0.693 × 0.87 × 1000 (mL/min)]/T1/2 and normalized GFR= GFR × 1.73/surface area (SA) (mL/min/1.73 m^2), where VD is the volume of distribution and T1/2= inversely elimination constant. It is necessary to make a correction to body surface area normalization of 1.73 m^2, it was made using the Haycok formula [19].

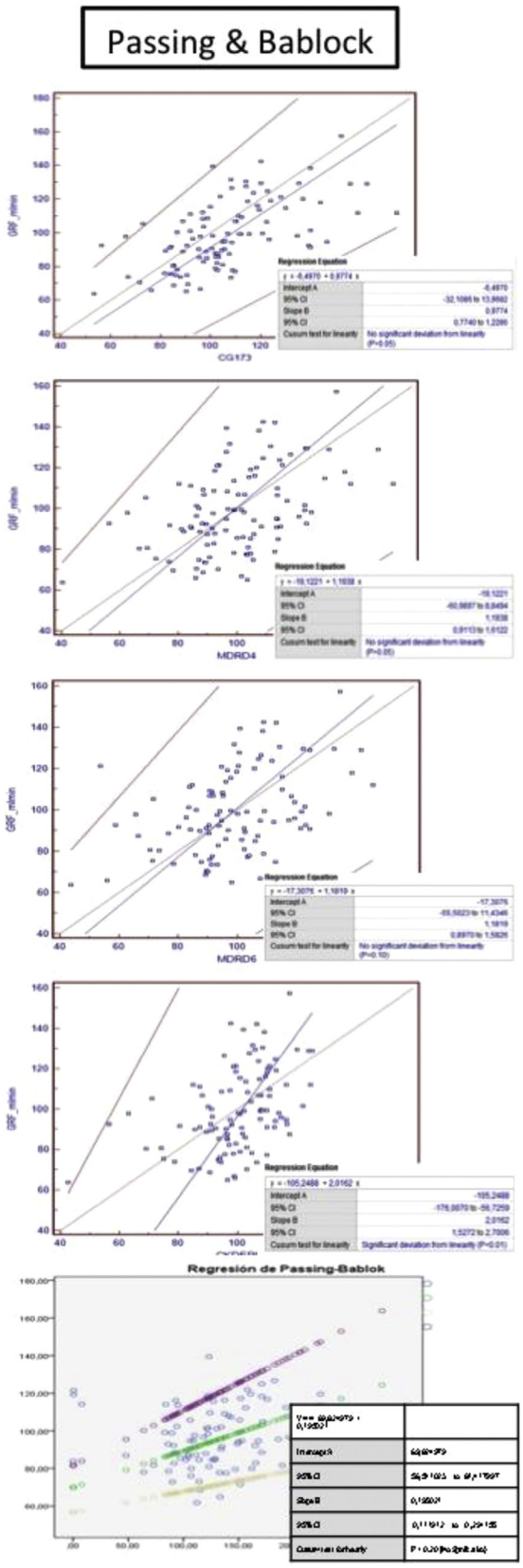
Creatinine Clearance

It is important to properly collect a 24-hour urine. It is correct if the creatinine in the 24-hour urine is between 15 and 20 mg/kg for women and 20 and 25 mg/kg for men. We evaluated the means of 2 samples collected by the donor. CrCl_[UCr_V]/SCr (then adjusted for BSA of 1.73 m^2), where UCr_24-hour urine creatinine level and V_24-hour urine volume.

eGFR

The formulas used for the GF are as follows:

Cockcroft-Gault: [(140_age) _weight (kg)]/[SCr_72] _ [0.85 if female] (adjusted for BSA of 1.73 m^2).



MDRD-4: 186 × (creatinine) − 1.154 × (age) − 0.203 × (0.742 if female).

MDRD-6: 170 × (creatinine) − 0.999 × (age) − 0.176 × (urea x 0.467) − 0.170 × (albumin) 0.318 × (0.762 if female) × (1.180 if black race).

CKD-EPI equation was calculated as gender specific and stratified by creatinine levels, according to reference [11].

To calculate the BSA we have used the Monsteller formula (√height (cm)*weight (kg)/3600).

The serum creatinine was determined using automatic tests established in routine laboratories through the Jaffe Method with alkaline picrate on Roche/Hitachi cobas systems.

Statistical Analysis

The descriptive data from the sample have been analysed using SPSS19.00. Bland-Altman graphics were used to represent the error trend between mGFR and eGFR with the average of the global media with 2SD, in addition to using the Passing & Babblok for the nonparametric analysis in the comparison of the equivalence between both methods to calculate the GF. This method uses the gradient of the regression line calculated as the mean of all possible slopes.

RESULTS

From the 105 potential living kidney donors studied, 69 were females (65.7%), with an average age of 47.65 ± 10.94 years. Mean body area 2.04 ± 0.54 m^2, urinary volume in 24-hours for the CCr was 1804.34 ± 767.6 mL/min with 92 (87.6%) valid samples to determine and average CCr of 130.78 ± 49.07 mL/min/1.73 m^2. The mGFR mean was 96.22 ± 16.44 mL/min/1.73 m^2 by EDTA-Cr51. eGFR mean according to the Cr-based formulas was: Cockcroft-Gault, 106.57 ± 22.42 mL/min/1.73 m^2; MDRD-4, 100.14 ± 18.51; MDRD-6, 99.03 ± 18.95; and CKD-EPI, 99.80 ± 13.89. We compared the mGFR by EDTA-Cr51 with the formulas bases on CR observing the following results. Figs 1 and 2 show the comparison of the mGFR using 51Cr-EDTA between eGFR with the different formulas and with CCr in 24-hour urine. Through the Bland-Altman graphic we observe dispersed values of the generalized form by the different formulas showing extreme values, out from the 1.96 standard deviation (SD), in CCr and CKD-EPI (Fig 1). In the rest of the formulas, although values are dispersed, they are within 1.96 SD or close to it. In Fig 2, through Passing & Bablok we objectify that the formulas with the closest approximation to the mGFR reference method are the el MDRD-4 (slope B is 0.93 with an IC of 95% from 0.74–1.13) and MDRD-6 (slope B is 0.85 with a IC of 95%

Fig 2. Through Passing & Bablok we objectify that the formulas with the closest approximation to the mGFR reference method are the el MDRD-4 (slope B is 0.93 with an IC of 95% from 0.74–1.13) and MDRD-6 (slope B is 0.85 with a IC of 95% from 0.69–1.08). C-G shows a slope B of 0.73 with in IC of 95% (range, 0.58–0.89). Revealing a high dispersion by means CCr with a slope B of 0.29 (IC 95%; range, 0.19–0.40) and CKD-EPI with slope B of 1.41 (IC 95%; range, 1.13–1.78).

from 0.69–1.08). C-G shows a slope B of 0.73 with in IC of 95% (range, 0.58–0.89). Revealing a high dispersion by means CCr with a slope B of 0.29 (IC 95%; range, 0.19–0.40) and CKD-EPI with slope B of 1.41 (IC 95%; range, 1.13–1.78).

DISCUSSION

In the last decades both the average age of living donors and their cardiovascular comorbidity (advanced age, pre-hypertension, blood hypertension, obesity level I, and hydrocarbonated intolerance) have constantly increased due to new requirements for the inclusion criteria. These potential donors present more long-term risk of progressively losing their renal function after donation. Therefore, a more precise and rigorous evaluation of their kidney function is recommended, although nowadays no standard criteria exist for these patients.

The Amsterdam Forum established a CCr <80 mL/min/1.73 m^2 to disregard donation, not considering gender or age, this criteria was modified with a low limit of 2 SD under normal for age, gender or body area corrected for 1.73 m^2. Nevertheless, the British guide [14] analysed 28 donors, proposing that the minimum admissible function should be established based on the age of the donor. Thus the minimum GF required to donate would be such that will allow the donor to reach 80 years with a GF of at least 37.5 mL/min/1.73 m^2 (although the lack of evidence about real evolution is recognized, especially for donors older than 60 years). Accepting that after donation GF is recovered in around 70% of the predonation number and the renal function lost rate is 0.9 mL/min/1.73 m^2 per year from 40- year-olds [13].

In our series, 6 potential kidney living donors had an eGFR using MDRD <80 mL/min/1.73 m^2; however, when making the mGFR using EDTA-51Cr was >80 mL/min/1.73 m^2, therefore, 5.71% of potential living kidney donors were excluded by eGFR using MDRD.

For all this, the kidney function study is decisive in the evaluation of possible kidney donors. In addition, after the nephrectomy the donor abruptly loses 50% of his or her GF, but it recovers very fast. In the first year the compensation from the remaining kidney was around 20%–40% of the split function; this is influenced by age, gender, race, and body size, although the major factor to determine the final GF reached is the prenephrectomy kidney function [15,16]. Although the reference measure of mGRF is the clearance of external markers, isotopic and nonisotopic, these methods are not always available; therefore, the classic CCr method with 24-hour urine continues to be the most common option. However, there is a significant variability on the results due to inaccurate urine collection.

Hence, the eGFR has been standardized with Cr serum–based formulas although these are not validated in a healthy population. Issa et al [10] evaluated CCr, MDRD, and CG in comparison with mGFR with 125 I-iothalamate in 423 living kidney donors, concluding that there was a variability in the results using different methods, with CCr being less accurate, underestimating GF, and having less correlation with the renal graft function.

In this study we have made a comparison among different methods, finding that for our sample MDRD-4 and MDRD-6 were the best options to supply the mGFR, although most of the studies of MDRD are poorly related to real GF in values >60 mL/min/1.73 m^2. On the other hand, we have observed that CCr in 24-hour urine could underestimate mGFR. The same occurs with eGFR by CG and CKD-EPI, this last underestimating mGFR.

In conclusion, eGFR for MDRD-4 and MDRD-6 formulas show the highest approximation to mGFR for EDTA-Cr51. This might represent the best option if the direct GF measure is not available. Although in most of the cases the eGFR would be enough, it is recommended to perform a direct measure of the GF in patients with risk factors for the development of a chronic kidney disease in the long term and in patients with an estimated renal function close to the acceptable limit for their age.

REFERENCES

[1] Recomendaciones de la Sociedad Española de Nefrología (S.E.N.) y de la Organización Nacional de Trasplantes (ONT) sobre trasplante renal de donante vivo. Nefrología 2010;30(Suppl. 2).

[2] Port FK, Merion RM, Wolfe RA, et al. Trends in organ donation and transplantation in the United States, 1997-2006. Am J Transplant 2008;8:911.

[3] Davis CL, Delmonico FL. Living-donor kidney transplantation: a review of the current practices for the live donor. J Am Soc Nephrol 2005;16:2098–110.

[4] Delmonico FL, Dew MA. Living donor kidney transplantation in a global environment. Kidney Int 2007;71:608–14.

[5] Poggio ED, Braun WE, Davis C. The science of stewardship: due diligence for kidney donors and kidney function in living kidney donation– evaluation, determinants, and implications for outcomes. Clin J Am Soc Nephrol 2009;4:1677–84.

[6] Velosa JA, Offord KP, Schroeder DR. Effect of age, sex, and glomerular filtration rate on renal function outcome of living kidney donors. Transplantation 1995;60:1618–21.

[7] Poggio ED, Wang X, Greene T, Van Lente F, Hall PM. Performance of the Modification of Diet in Renal Disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease. J Am Soc Nephrol 2005;16:459–66.

[8] Rule AD, Gussak HM, Pond GR, Bergstralh EJ, Stegall MD, Cosio FG, et al. Measured and estimated GFR in healthy potential kidney donors. Am J Kidney Dis 2004;43:112–9.

[9] Poggio ED, Rule AD, Tanchanco R, et al. Demographic and clinical characteristics associated with glomerular filtration rates in living kidney donors. Kidney Int 2009;75:1079–85.

[10] Alcázar R, Albalate M. Nuevas fórmulas para estimar el filtrado glomerular. Hacia una mayor precisión en el diagnóstico de la enfermedad renal crónica. Nefrologia 2010;30:143–6.

[11] Issa N, Meyer KH, Arrigain S, Choure G, Fatica RA, et al. Evaluation of creatinine-based estimates of glomerular filtration rate in a large cohort of living kidney donors. Transplantation 2008;86:223–30.

[12] Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro 3rd AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.

[13] Delmonico F. Council of the Transplantation Society. A Report of the Amsterdam Forum on the Care of the Live Kidney Donor: Data and Medical Guidelines. Transplantation 2005;79(6 Suppl.):S53–66.

[14] Lumsdaine JA, Wigmore SJ, Forsythe JL. Live kidney donor assessment in UK and Ireland. Br J Surg 1999;86:877–81.

[15] Cohney S, Kanellis J, Howeell M. Donor renal function. Nephrology 2010:15.

[16] Fleming JS, Zivanovic MA, Blake GM, Burniston M, Cosgriff PS. Guidelines for the measurement of glomerular filtration rate using plasma sampling. Nuclear Medicine Communications 2004;25:759–69.

[17] Mistry R. Manual of Nuclear Medicine Procedures. Cap 2. Chapman and Hall Ltd; 1988.

[18] Chantler C, Garnett ES, Parsons V, Veall N. Glomerular filtration rate measurement in man by the single injection method using 51Cr-EDTA. Clin Sci 1969;37:169–80.

[19] Haycock GB, Schwarz GJ. Geometric method for measuring body surface area. A height-weight formula validated in infants. J Paediat 1978;93:62–6.