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Study of Renal Function in Living Kidney Donors: Estimated or Measured Glomerular Filtration

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ABSTRACT

Introduction. In living kidney donations the accuracy of renal function is fundamental, especially for potential donors who have limited renal function (creatinine clearance levels [CCr] <90 mL/m/1.73 m^2), are >50 years old, and who have cardiovascular risk factors that might favor the development of kidney diseases.

Objective. To compare the direct measured glomerular filtration (mGFR) using 51Cr-EDTA and the estimations based on creatinine (estimated glomerular filtration rate [eGFR]): CCr with 24-hour urine, and estimated using Cockroft-Gault (adjusted using body surface area, Mosteller formula), modification of diet in renal disease−4 (MDRD-4), MDRD-6, and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) to determine the usefulness of different methods to evaluate the kidney function.

Patients and Methods. The kidney function evaluation was performed for 37 potential kidney donors using the 51Cr-EDTA method. The GFR obtained through the 51Cr-EDTA was compared with the CCr values in 24-hour urine and eGFR based on creatinine (Cockcroft-Gault, MDRD-4, MDRD-6, and CKD-EPI).

Results. Using the Bland Altman graph, the most dispersed results were obtained with the eGFR using CCr in 24-hour urine and CKD-EPI. By means of Passing and Bablok, MDRD-4 and MDRD-6 showed the highest approximation to the reference method proposed to be substituted, whereas CCr showed a high dispersion.

Conclusion. The eGFR using MDRD-4 and MDRD-6 formulas revealed the best adjustment to the measure by 51Cr-EDTA. This might represent the best option if a direct eGFR measure is not available.

KIDNEY transplantation is the best treatment for terminal kidney failure. The main barriers limiting this therapy are the shortage of deceased donors and the comorbidity of the patients suffering from kidney failure that prevent the transplantation. Living-donor kidney transplantation allows us to overlook the lack of organs from deceased donors and shows better results than cadaver transplantation.[1] Currently, the donation age is increasing; the proportion of patients older than 50 years has doubled in the last 20 years.[2,3] Many transplantation teams receive donors with high blood pressure, obesity, and other potentially harmful issues to the kidneys. Consequently, it is necessary to reach the most accurate estimation of the kidney function, aiming to avoid the long-term development of nephropathy related with initial decreased kidney function. The measured glomerular filtration rate (mGFR; measured through non-isotopic external markers [inulin, iohexol, iothalamate] or isotopic techniques [125I iothalamate, 51Cr-EDTA, 99Tc DTPA]) has been considered the gold standard for the evaluation of kidney failure. Nonetheless, these are not available in many medical centers because of their complexity. The estimated GFR (eGFR) with 24-hour urinary creatinine clearance (CCr) is frequently used because of its availability. However, this requires a 24-hour urine collection, which is laborious

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0041-1345/13/$–see front matter
http://dx.doi.org/10.1016/j.transproceed.2013.10.022

and frequently mistaken. The eGFR using serum-based creatinine formulas (Cockroft-Gault, aMDRD, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) is not validated for this specific population because these come from a population with a lower rate of glomerular filtration.[6,7] One of the main limitations of the eGFR using MDRD is its low correlation with the real glomerular filtration for values higher than 60 mL/min/1.73 m^2. Nonetheless, the average CCr and MDRD give a good approximation to the mGFR with 125 iothalamate.[8] Dr Levey, from the CKD-EPI group of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), creator of the MDRD equation, has recently published a new equation. This new equation is more accurate and has been validated in the American population, the CKD-EPI, based on the standardized creatinine and using the same parameters as the MDRD equation (sex, race, and age).[8] This equation aims to achieve a better performance in the normal and higher ranges of glomerular filtration. Nevertheless, the accuracy of this equation in living donors, especially in older people, has not been proven.

Because of the complexity of the direct measurement of glomerular filtration, and the fact that not all centers have a validated technique, we performed a comparative study between the mGFR with 51Cr-EDTA for the measurement of endogenous creatinine and the eGFR by means of serum creatinine–based formulas.

MATERIALS AND METHODS

We evaluated 37 potential living kidney donors from April 2011 to January 2013 in the Virgen del Rocio University Hospital. The mGFR was determined using the clearance of 51Cr-EDTA and the eGFR by CCr in 24-hour urine and serum creatinine–based formulas before donation as part of the screening program.

Measured GFR

Based on the recommendations of the British Society of Nuclear Medicine[13] for the calculation of the glomerular filtration, we applied the second exponential method, according to Mistry, with Chantler's correction.[14] Thus, GFR = [VD × 0.693 × 0.87 × 1000 (mL/min)]/T1/2 and normalized GFR = GFR × 1.73 /body surface area (BSA; mL/min/1.73), where VD is the volume of distribution and T1/2 is an inverse elimination constant. It is necessary to make a correction to BSA normalization of 1.73 m^2. The calculation of the BSA of the patient was made using the Haycock formula.

Creatinine Clearance

Proper collection of a 24-hour urine sample is important. It was considered correct if the creatinine in the 24-hour urine was between 15 and 20 mg/kg for women and 20 and 25 mg/kg for men. The means of two samples were collected per donor: CrCl_ [UCr_V]/SCr (then adjusted for BSA of 1.73 m^2), where UCr_24-hr urine creatinine level and V_24-hr urine volume. The formulas used for eFGR were the following:

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 × 0.467)-0.170 × (albumin) 0.318 × (0.762 if female) × (1.180 if black race)

The CKD-EPI equation was calculated to be gender specific and stratified by creatinine levels, according to Delmonico et al.[9–11]

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

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

Statistical Analysis

The descriptive data from the sample were analyzed using SPSS19.00 (IBM, Chicago, Ill, United States). Bland-Altman graphs were used to represent the error trend between mGFR and eGFR with the average of the overall mean with 2 SDs, in addition to using Passing and Bablok for the non-parametric analysis in the comparison of the equivalence between both methods to calculate the GFR. This method uses the gradient of the regression line calculated as the mean of all possible slopes.

RESULTS

Of the 37 potential living-kidney donors studied, 23 were female (62.2%) and 14 male (37.8%), with an average age of 47.95 ± 10.93 years. The mean body area was 1.81 ± 0.18 m^2, mean serum Cr level 0.75 ± 0.16 mg/dL, and the 24-hour urinary volume for the CCr was 1921.75 ± 884.18 mL/min with 27 (71%) valid samples to determine and an average CCr of 148 ± 62.75 mL/min/1.73 m^2. The mean mGFR was 99.21 ± 17.58 mL/min/1.73 m^2 by 51Cr-EDTA. The mean eGFR according to the Cr-based formulas was Cockcroft-Gault, 110 ± 22.9 mL/min/1.73 m^2; MDRD-4, 103.36 ± 17.90; MDRD-6, 103.99 ± 17.56; and CKD-EPI, 102.47 ± 12.34. We compared the mGFR by 51Cr-EDTA with the formulas based on Cr. Figure 1 shows the comparison of the mGFR using 51Cr-EDTA between eGFR with the different formulas and with CCr in 24-hour urine. The Bland and Altman graph shows the dispersion values of the generalized form by the different formulas with extreme values outside the 1.96 SD in CCr and CKD-EPI. Although the values were dispersed, the rest of the formulas were within 1.96 SD or close to it. In Fig 1, with Passing and Bablok, we see that the formulas with the closest approximation to the mGFR reference method are the MDRD-4 (slope B is 0.96 with a 95% confidence interval [CI] of 0.68–1.44) and MDRD-6 (slope B is 0.99 with a 95% CI of 0.60–1.5). The Cockcroft-Gault shows a slope B of 0.7 with a 95% CI of 0.45–1.19. There was a high dispersion by means of CCr with a slope B of 0.16 (95% CI, 0.029–0.34) and CKD-EPI with slope B of 1.54 (95% CI, 1.01–2.8).

DISCUSSION

The study of kidney function is decisive in the evaluation of possible kidney donors because of the influence on implant functionality and the donor's remaining kidney. After nephrectomy, the donor abruptly loses 50% of their glomerular filtration, but the donor recovers very fast, mainly

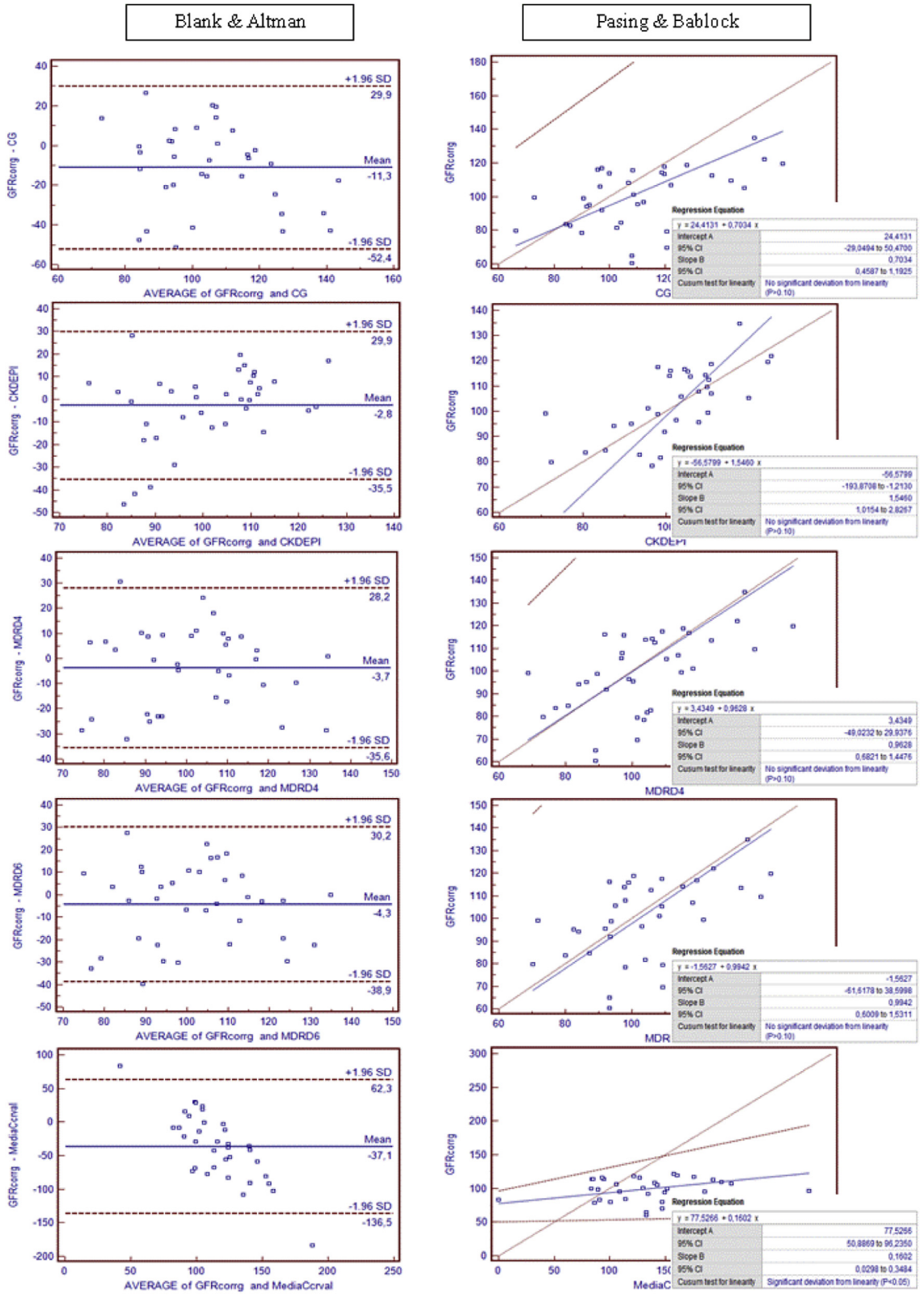

Fig 1. Show the comparison of the mGFR using 51Cr-EDTA between eGFR with the different formulas and with CCr in 24-hour urine.

during the first week. After the first year, the compensation from the remaining kidney is approximately 20% to 40% of the split function; this is influenced by age, sex, race, and body size, although the major factor determining the final GFR reached is the prenephrectomy kidney function.[4,5] Although the reference method for the mGFR is the clearance of external markers, isotopic and non-isotopic, 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 significant variability in the results due to inaccurate urine collection. In our sample, the urine collection was accurate in only 27 of the patients (71%). Hence, the eGFR has been standardized with serum Cr–based formulas, even though these are not validated in the healthy population. Issa et al[8]evaluated CCr, MDRD, and Cockcroft-Gault in comparison with the mGFR with 125 I-iothalamate in 423 living kidney donors. They concluded that there was variability in the results using the different methods, with CCr being the less accurate, underestimating GFR, and having less correlation with the renal graft function. In this study we found that MDRD-4 and MDRD-6 were the best options to provide the GFR in our sample, even though most studies of MDRD are poorly related to real GFR in values >60 mL/min/1.73 m^2. On the other hand, we observed that CCr in 24-hour urine could not substitute the mGFR, considerably underestimating it. The same was found for the eGFR by Cockcroft-Gault and CKD-EPI, the latter underestimating the mGFR.

In the last decades, not only has the average age of living donors constantly increased, so has their cardiovascular comorbidity (advanced age, pre-hypertension, hypertension, obesity level I, and carbohydrate intolerance) because of new inclusion criteria. These potential donors present a greater 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 currently 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 sex or age. This criterion was modified with a low limit of 2 SD less than normal for age, sex, or body area corrected for 1.73 m^2. Nevertheless, the British guide[12] analyzed 28 donors and proposed that the minimum admissible function should be established based on the age of the donor. Thus, the minimum GFR required to donate would be such that will allow the donor to reach 80 years with a GFR 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 GFR is recovered to approximately 70% of the pre-donation state and the renal function loss rate is 0.9 mL/min/1.73 m^2 per year from 40 years old.[13,14]

In our series, two potential living-kidney donors had an eGFR using MDRD <80 mL/min/1.73 m^2, although when calculating the mGFR using 51Cr-EDTA it was >80 mL/min/1.73 m^2; therefore, 5.4% of potential living-kidney donors were excluded by eGFR using MDRD.

CONCLUSION

The eGFR for MDRD-4 and MDRD-6 formulas shows the highest approximation to the mGFR by 51Cr-EDTA. This might represent the best option if the direct GFR measure is not available. Although in most cases the eGFR would be enough, it is recommended to perform a direct measurement of the GFR in patients with risk factors for the development of chronic kidney disease in the long term and in patients with an estimated renal function close to the limit acceptable for their age.

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