

Predicted and Measured Creatinine Clearance for the Estimation of Renal Graft Function: New Tools from Body Composition Analysis

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Abstract

Aim of this study was to evaluate, in Renal Transplant Recipients (RTR), a new method to predict Creatinine Clearance (Ccr) from Plasma Creatinine (Pcr) and from the value of Body Cell Mass (BCM).

The values of BCM were obtained, from body impedance analysis (BIA) using an impedance plethysmograph, in 87 RTR with different graft function. The ratios of 24-hour Urinary Creatinine Excretion (Ucr) over BCM were calculated in 30 RTR. In the remaining 57 RTR, Ccr was predicted from Pcr and individual values of BCM (BCM Ccr), using the mean ratio Ucr/BCM found in the first group of patients. In the same patients, Ccr was predicted according to Cockcroft and Gault (CG Ccr). The mean of triplicate measurement of 24-hour Ccr (24 h Ccr), obtained by the standard formula $Ucr \times Vol/min/Pcr$, was used as the reference value of renal graft function.

BCM Ccr had a better agreement with 24 h Ccr than CG Ccr, particularly in patients with graft failure.

Thanks to its simplicity, accuracy and reproducibility, BCM Ccr is more suitable than 24-hour Ccr to estimate graft function. In the meantime, the body composition data gives useful information for the evaluation of nutritional status and of the equilibrium of body fluid compartments.

Keywords: Renal graft function; Creatinine clearance; Estimate of renal function; Electrical body impedance; Body composition analysis; Body cell mass

Introduction

The “gold standard” method to assess renal graft function is the direct measurement of glomerular filtration rate (GFR) from the value of inulin clearance or of other glomerular tracers (51Cr-EDTA, 99mTc-DTPA). Since the measurement of inulin clearance is cumbersome and radioisotopic methods are not universally available, renal graft function is commonly evaluated by measuring plasma creatinine (Pcr) or creatinine clearance (Ccr). Pcr is a very simple and highly reproducible test. Unfortunately, it has a poor sensitivity, which does not allow to ascertain a reduction in renal function of a minor degree, and a temporal delay in case of acute variations in GFR. Furthermore, plasma concentration of creatinine, besides GFR, is influenced by body composition, namely the amount of muscle mass. On the other hand, the usefulness of Ccr in the evaluation of renal function is greatly reduced by the high variability of its measurement, mainly due to the difficulty in obtaining an accurate collection of 24-hour urine [1,2]. Repeated measurements of this test, one day apart, allow to meliorate the accuracy of Ccr. Aiming to simplify the procedure and to avoid the need for urine collection, different methods have been proposed to estimate Ccr from Pcr [3,4]. Other formulas have been proposed to estimate directly GFR in Chronic Kidney Disease (CKD) patients. However, it is uncertain if they are also suitable to estimate graft function in Renal Transplant Recipients

(RTR). Thus, in the follow-up of RTR remains a need for simple and accurate tests for assessing graft function.

The aim of this study was to evaluate the possibility of estimating graft function in RTR by using a new method that avoids urine collection. This method estimates Ccr, and possibly GFR, by combining the level of Pcr with the value of body cell mass (BCM). BCM can be measured with a tetrapolar impedance plethysmograph from the values of electrical body resistance and reactance. Total Body electrical Impedance Analysis (BIA) is commonly used to analyze body composition in renal patients [5-7]. Muscle mass, which produces creatinine, is the major constituent of BCM. The rationale of the proposed method to estimate graft function is that 24-hour Urinary Creatinine Excretion (Ucr) can be predicted from the value of BCM. This seems probable since the amount of 24-hour Ucr is an estimate of Fat-free Mass (FFM) and muscle mass [8,9]. Furthermore, our previous data demonstrated that in CKD patients with different kidney diseases and various degrees of renal function it is possible to predict Ccr from the values of FFM and BCM combined with plasma creatinine levels [10]. In particular, Ccr predicted from the values of BCM has a better agreement with GFR than the 24-hour measured Ccr, at every level of renal function [11]. In CKD patients it was also possible to predict the value of GFR from Pcr and BCM values [12].

Patients and Methods

Patients

Eighty-seven renal transplant recipients (F 32, M 55) aged 22-63 years, transplanted since 2 weeks-17.1 years, with different degrees of

renal graft function (Pcr 0.9-6.3 mg/dl, mean 2.06 mg/dl), stable during the study period, were randomly divided in two groups, one of 30 and the other of 57 patients. Exclusion criteria were: age<18 years, inability or refusal to express informed consent, modifications in immunosuppressive regimen or administration of other potentially nephrotoxic drugs in the two weeks preceding the study, and/or instability of renal graft function during the study period.

The clinical data of the two groups of patients were very similar (Table 1).

	All Patients	Group 1	Group 2
No (F/M)	87 (32/55)	30 (12/18)	57 (20/37)
Age, years	22-63, 43.1	22-63, 44.4	22-60, 42.4
Transplant age, years	0.03-17.1, 101.05 1.05	0.04-8.0, 0.66	0.03-17.1, 1.3
Plasma creatinine, mg/dl	0.9-6.3, 2.06	0.9-6.3, 1.98	0.9-4.6, 2.10
Height, cm	140-184, 166.3	149-183, 165.3	140-184, 166.8
Body weight, kg	38.8-99.0, 68.4	44.4-93.4, 65.8	38.8-99.0, 69.8
Body surface, m ²	1.22-2.19, 1.76	1.36-2.01, 1.72	1.22-2.19, 1.78
Body mass index, kg/m ²	17.5-38.0, 24.7	18.4-34.1, 24.1	17.5-38.0, 25.0

Table 1: Main clinical and anthropometric data of renal transplant patients (range and mean values).

All patients gave their informed consent to participate to the study. This investigation was conducted in accordance with the ethical guidelines proposed by the Declaration of Helsinki.

Body composition analysis: measurement of body cell mass

Total body electrical impedance was measured with a tetrapolar impedance plethysmograph (BIA 109-Akern, Firenze, Italy) in patients lying supine, while fasting. Two electrodes were placed on the dorsal surface of the right hand, and two, on the dorsal surface of the right foot [6]. The analysis of single frequency electrical impedance (0.8 mA, 50 KHz) gives the values of resistance and reactance. BCM was calculated, according to manufacturer's equation, from the values of resistance and reactance combined with body height and weight (Table 2).

Relationship between 24-hour urinary creatinine excretion and body cell mass

The relationship between 24-hour Ucr and BCM was evaluated in the 30 renal transplant patients of group 1. The patients were instructed to collect 24-hour urine for 3 days, to improve the accuracy of 24-hour urinary creatinine measurement. Urinary creatinine concentration was determined with a standard autoanalyzer method (Boehringer Mannheim automated analysis for Hitachi 717/911) and the value of 24-hour Ucr was measured for each daily collection. The ratios between 24-hour Ucr (mg/24-hour, mean of the 3 measurements) and the value of BCM (kg) were then calculated for

each patient. To calculate the mean 24-hour Ucr of individual patients, a single value of 24-hour Ucr was discarded if it differed more than 20% from the mean of the two other values.

Number	All Patients 87	Females 32	Males 55
Resistance, Ohm	350-852, 540.4	429-852, 571.3	350-661, 522.5
Reactance, Ohm	20-80, 46.1	20-80, 46.0	25-73, 46.2
BCM, kg	9-36, 22.5	9-32, 18.4	17-36, 24.8
BCM, % BW	19-46, 32.9	19-41, 29.2	22-46, 35.1
FM, kg	5-38, 17.2	9-38, 19.4	5-38, 15.9
FM, kg/BW	7-45, 24.8	17-39, 29.8	6.9-45.1, 21.9
TBW, kg	22-52, 38.6	22-42, 32.4	33-52, 41.1
TBW, kg/BW	41-74, 56.0	41-62, 52.1	46-73, 58.3
ECW, kg	9-33, 18.2	9-33, 16.9	13-30, 30.3
ECW, kg/BW	17-48, 26.9	17-48, 26.9	19-47, 26.9

Table 2: Body impedance analysis in all 87 transplanted patients. Measurements of resistance, reactance and phase angle, Body Cell Mass (BCM), Fat Mass (FM), Total Body Water (TBW), and Extracellular Water (ECW). Values of body compartmentys are reported as absolute values (kg), as percentage of body weight (%BW) (ranges and mean values).

Prediction of creatinine clearance from body composition analysis

In the second group of 57 renal transplant recipients Ccr was predicted from individual values of plasma creatinine and BCM, using the mean ratios 24-hour Ucr/BCM, found in the first group of 30 transplanted patients (Table 3). Plasma creatinine concentration was measured with a standard autoanalyzer method (Boehringer Mannheim automated analysis for Hitachi 717/911). BCM Ccr was calculated as follows:

$$\text{BCM Ccr (ml/min)} = \frac{\text{BCM (kg)} \times \text{the mean ratio 24-hour Ucr/BCM (mg/kg)}}{\text{Pcr (mg/ml)} \times 1440 \text{ min}}$$

It is important to note that the numerators of the above formula give the value of 24-hour Ucr (mg/24-hour) estimated from the individual value of BCM.

Example of calculation of BCM Ccr

Patient # 7, male, height=173 cm, body weight = 87.0 kg.

Measured 24-hour Ccr=31 ml/min

Pcr = 2.83 mg/dl = 0.0283 mg/ml

BCM = 24.4 kg

BCM Ccr = 24.4 kg × 52.4 mg/kg=31 ml/min

0.0283 mg/ml × 1440 min

52.4 mg/kg is the mean ratio of 24 hr Ucr over BCM obtained in the male patients of group 1 (Table 3).

Prediction of creatinine clearance from plasma creatinine

In the 57 transplanted patients of group 2 Ccr was also predicted from Pcr according to Cockcroft and Gault (CG Ccr) [3].

	Females	Males
Number of patients	12	18
24 h Ucr/BCM (mg/kg)	54.1±11.3	52.4±9.6

Table 3: Mean ratios (\pm SD) of 24-hour urinary creatinine excretion over body cell mass (24 h Ucr/BCM, mg/kg) in the 30 renal transplant patients of group 1.

Measurement of 24-hour creatinine clearance

As the reference value, 24-hour Ccr was measured three times in all 50 transplanted patients of group 2, by collecting 24-hour urine, and was calculated with the standard formula. The measurement of 24-hour Ccr was performed for three days, to achieve a good accuracy of its measurement. To calculate the mean 24-hour Ccr of individual patients, a single value of 24-hour Ccr was discarded if it differed more than 20% from the mean of the two other values.

Repeatability of the measurements

The repeatability of the measurements of resistance and reactance, BCM, and body weight were evaluated on duplicate measures performed on two different days, within one week, in 40 other renal patients (21 females, 19 males; aged 19-81 years; body weight 46-89 kg).

Statistical analysis

The correlation and the agreement [13] between predicted and measured Ccr were tested. Single and multivariate regression analysis was performed among 24-hour Ucr, BCM, body weight, height and age. Student t-test was employed to evaluate the statistical significance of the differences between the mean values of different groups of data. A p-value lower than 0.05 was considered statistically significant.

Results

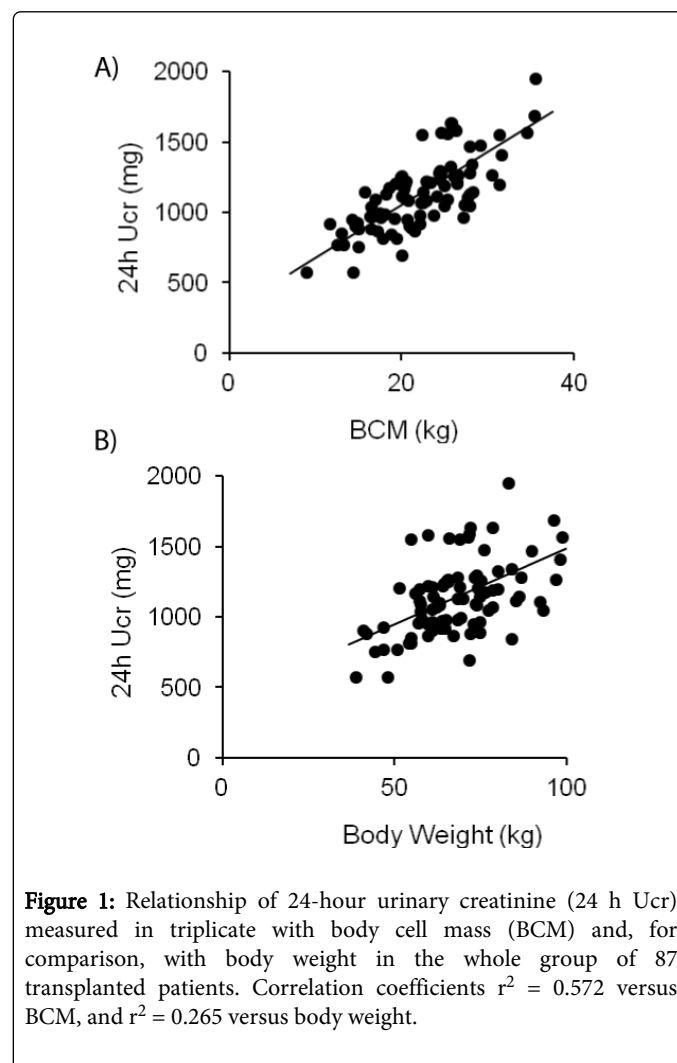
Body composition analysis: measurement of body cell mass

The results of the measurement of BCM in all 87 transplanted patients are reported in Table 2. Values of BCM were expressed as absolute values and as percentage of body weight. Higher values were found in males than in females. Electrical measures (resistance and reactance) and the measures of fat mass, total body water and extra-cellular water, calculated from BIA are reported in Table 2.

Relationship between 24-hour urinary creatinine excretion and body cell mass

A statistically significant correlation between 24-hour Ucr and BCM ($p < 0.0000001$) was found in the whole group of 87 transplanted patients (Figure 1). The correlation between 24-hour Ucr and body weight was significantly weaker than that with BCM. The results of the single and multivariate regression analysis among 24-hour Ucr, BCM, body weight, height and age of patients indicate that BCM justifies 57.2% of the variability of Ucr. The coefficient of determination increased modestly (from 0.572 to 0.618) with the introduction of age

and height, while did not change introducing the body weight in the regression.



The ratios (mean \pm SD) of 24-hour Ucr over BCM, calculated separately for male and female patients, are reported in Table 3. These values represent the amount of creatinine, in milligrams, that is excreted in the 24-hour urine per kilogram of BCM.

Prediction of creatinine clearance

The relationship between predicted clearances and 24-hour Ccr (mean of 3 measures) in the 57 renal transplant recipients of group 2 is shown in Figure 2. The correlation of BCM Ccr with 24-hour Ccr was stronger than that of CG Ccr with 24-hour Ccr, as indicated by the values of correlation coefficients, slopes and intercepts (Figure 2, upper part). The agreement between predicted clearances and 24-hour measured Ccr, evaluated according to Bland and Altman [2], was stronger for BCM Ccr (Figure 2, lower part). The mean difference (\pm SD) between BCM Ccr and 24h Ccr was 0.46 ± 7.40 ml/min/ 1.73 m² (NS), while between CG Ccr and 24 h Ccr it was 3.05 ± 8.24 ml/min/ 1.73 m² ($p < 0.05$). The differences between BCM Ccr and 24-hour Ccr were symmetrically distributed around the 0 difference (Figure 3). On the contrary, the frequency distribution of the differences between CG

Ccr and 24-hour Ccr was asymmetrical, skewed to the right, thus confirming the overestimation of 24 h Ccr by CG Ccr (Figure 3).

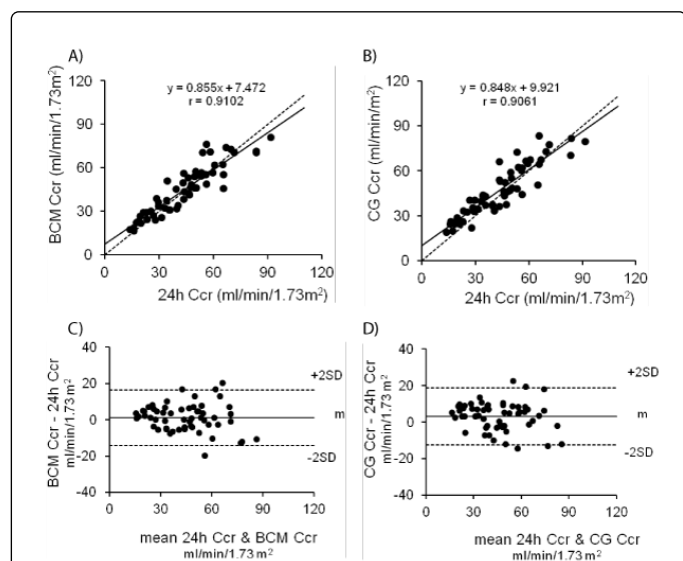


Figure 2: Relationship between predicted clearances and measured 24-hour creatinine clearance in the 57 transplanted patients of group 2. Correlation (upper part) and agreement plots (lower part) are reported. BCM Ccr=Creatinine Clearance predicted from BCM; CG Ccr=Creatinine Clearance predicted according to Cockcroft and Gault; 24-hour Ccr=24-hour Creatinine Clearance (mean of three measures).

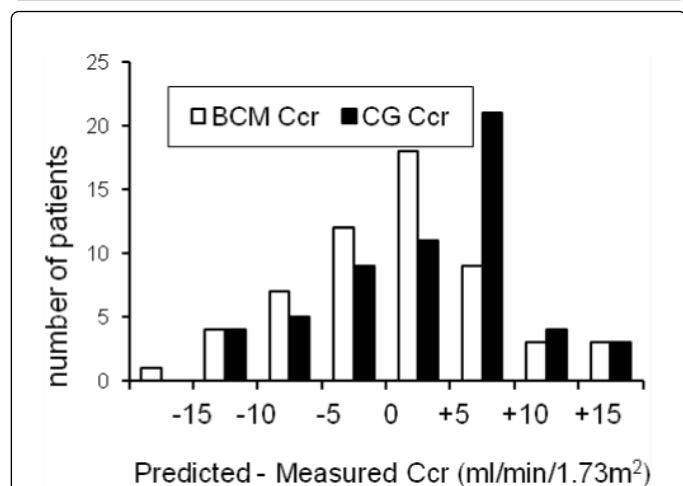


Figure 3: Histograms of frequency distribution of the differences between measured 24-hour creatinine clearances and predicted clearances. BCM Ccr=Creatinine Clearance predicted from BCM; CG Ccr=Creatinine Clearance predicted according to Cockcroft and Gault.

The relationship between predicted clearances and 24-hour Ccr (mean of 3 measures) was then considered separately for the 35 transplanted patients with decreased graft function (plasma creatinine >1.5 mg/dl, >132.6 mol/l). The correlation of BCM Ccr with 24 h Ccr was also very high (r=0.909) in this group of patients, while

the correlation of CG Ccr with 24 h Ccr resulted weaker (r=0.808) than in all 50 transplanted patients. Clearances predicted from BCM were found to better agree with 24 h Ccr in this group of patients with suspect graft failure as well. The mean difference (± SD) between BCM Ccr and 24 h Ccr was 1.45 ± 5.74 ml/min/1.73 m² (NS), while between CG Ccr and 24 h Ccr it was 2.92 ± 8.00 ml/min/1.73 m² (p<0.05).

Repeatability of the measurements

The repeatability of body composition analysis and of BCM Ccr, tested on two different days within one week, was quite good (Table 4).

	Coefficient of variation %
Resistance	3.5
Reactance	8.3
Body Cell Mass	3
Body weight	1.1
BCM Creatinine clearance	6.8

Table 4: Coefficients of variation (%) of duplicate measurements of body impedance, body cell mass, body weight, creatinine predicted from body cell mass (BCM). The measures were performed on two different days (within one week) in 40 renal patients.

Discussion

Ischemic, toxic or immunologic insults to the transplanted kidney are frequent and can cause acute or chronic graft dysfunction and lead to a nephropathy, which progresses to graft loss. The early recognition of graft functional impairment may be useful to stop the development and progression of injury [14]. For this purpose, there is a need for precise, accurate, reproducible and simple methods, suitable for repeated measurements, to assess kidney graft function. Unfortunately, none of the methods currently used to evaluate glomerular filtration rate fulfills these requirements. Furthermore, particular problems are found in estimating kidney function in renal transplant recipients [15,16].

The measurement of plasma creatinine concentration is the simplest method to evaluate renal function and has a good reproducibility. However, it is quite insensitive. Furthermore, due to the hyperbolic relationship between Pcr and GFR, the measurement of Pcr allows only a gross estimation of GFR. Finally, besides the rate of glomerular filtration, plasma concentration of creatinine also depends on the rate of creatinine production and on its volume of distribution; as a consequence it is influenced by the amount of muscle mass and of total body fluids of the individual patients.

Inulin clearance is the gold standard to measure GFR in man but it is not feasible to clinical practice. In fact, the commonly used method to measure inulin clearance is cumbersome and not well accepted by the patients due to continuous iv infusion of inulin, necessary for maintaining a constant plasma concentration, and to bladder catheterization, necessary for accurately collecting the urine. Other methods, which measure the clearance of radioactive tracers, such as 99mTc-DTPA [17], are precise and accurate but are expensive, somewhat complicated and not available everywhere.

Due to the problems reported above, creatinine clearance remains the most commonly used test to evaluate renal function in clinical practice, in renal transplant patients as well. However, the usefulness of Ccr is greatly reduced by its low precision and accuracy. The low precision is due to the high variability of measurements, and the low accuracy, to the overestimation of GFR by Ccr. The high variability of Ccr measurement is primarily due to incorrect collection of 24-hour urine and, secondarily, to the variability of urinary creatinine excretion [2]. In order to improve the accuracy of 24-hour Ccr, in the present study the measurements of this test were performed in triplicate.

In order to reduce the variability of Ccr measurements, different methods to predict Ccr from Pcr and some anthropometric data, thus avoiding urine collection, have been proposed [3,4]. The method proposed by Cockcroft and Gault is probably the most frequently employed and different authors believe that it accurately predicts 24-hour Ccr and/or GFR [18]. However, in some groups of patients, like obese, malnourished, edematous, elderly patients or those with renal failure or liver disease, the predicted clearances do not completely agree with measured clearances or with GFR [19-21]. Conflicting results have been reported in renal transplant patients regarding the accuracy of prediction of 24-hour Ccr using the method of Cockcroft and Gault [22-24]. In RTR the performance of urine-creatinine clearance and of many different prediction formulas has been found similar [14,25]. The comparison with isotopic measurement of GFR was often disappointing [26,27]. In particular, prediction errors of formulas are much higher in patients with better renal function [28]. However, in some situations prediction formulas are the only possible alternative to direct GFR measurement [29].

The results of our study indicate that CG Ccr significantly overestimate 24-hour Ccr in renal transplant recipients. A better agreement was found between 24-hour Ccr and BCM Ccr. The overall concordance (correlation and agreement) of BCM Ccr, predicted from body composition data, with 24-hour Ccr was stronger than that of CG Ccr, predicted from anthropometric data. The advantage of BCM Ccr over CG Ccr was even greater in those patients with graft dysfunction. In patients with graft failure the predicted clearances tend to overestimate 24-hour Ccr. This behavior, already reported for CG Ccr [19], was not statistically significant for BCM Ccr. Some degree of extra-renal elimination of creatinine occurs in patients with advanced renal failure [30]; therefore, in these patients the clearances predicted from Pcr overestimate the clearances obtained with the collection of urine.

The measurement of total body electrical impedance is a widely used method to evaluate body composition in renal patients, also in those with end-stage renal disease [5,7]. It is probably one of the least expensive methods to analyze body composition. The measurement of electrical body impedance is very simple, takes only a few minutes and is not inconvenient for the patients. Besides being simple, the estimate of creatinine clearance from body composition analysis is timesaving. In fact, it avoids the 24-hour period necessary to collect the urine and the determination of urinary creatinine.

The coefficient of variation of BCM measurements is very low (similar to the CV of body weight measurements). Furthermore, the CV of the clearances predicted from BCM is low (6.8%), very similar to that of plasma creatinine and definitely lower than that of single measurements of 24-hour Ccr (CV 22.4%). It is also important to note that BCM Ccr was found to be a more precise marker of GFR ($^{99m}\text{Tc-DTPA}$) than 24-hour Ccr [10].

The major limitation of this monocentric study is the modest number of patients examined, which limits the generalizability of the results.

Due to its better agreement with GFR, to the high reproducibility of its measurement, to its simplicity and low cost, the BCM Ccr is feasible to repeated measurements of graft function. An additional advantage of this method, based on body composition analysis, is the possibility to estimate, in the meantime, the nutritional status and the balance of fluid compartments.

In conclusion, it is possible to estimate renal graft function from body composition analysis and plasma creatinine concentration, thus avoiding urine collection. In particular, the clearances predicted from BCM have a better agreement with 24-hour measured creatinine clearance than clearances predicted with the Cockcroft and Gault formula. Thanks to its simplicity, precision, accuracy and reproducibility the proposed method seems more suitable than 24-hour creatinine clearance to evaluate graft function. Future studies will be aimed to evaluate in renal transplant recipients the possibility to estimate glomerular filtration rate from modifications of BCM Ccr formula.

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