Kidney & Blood Pressure Research

Kidney Blood Press Res 2014;39:668-676
DOI: 10.1159/000355813
Published online: December 19, 2014
Accepted: July 18, 2014

1423-0143/14/0396-0668$39.50/0

Original Paper

Cross-Sectional Evaluation of Kidney Function in Hospitalized Patients: Estimated GFR Versus Renal Scintigraphy

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Key Words
eGFR • CKD-EPI • MDRD • Renal Scintigraphy • RAS inhibitors

Abstract
Background/Aims: Accurate staging of chronic kidney disease (CKD) is very important. We tried to identify difference in GFR evaluation between CKD-EPI and Gates method with renal scintigraphy and which variables are associated with these differences. ***Methods:*** We retrospectively reviewed the records of 341 patients who underwent dynamic renal scintigraphy in the last 5 years. Patients were categorized according to KDIGO staging I to V, using the eGFR calculated with the CKD-EPI equation. Secondarily, we stratified patients according to treatment with renin-angiotensin system (RAS) inhibitors. ***Results:*** Gates method tends to underestimate GFR especially in CKD stage I (mean -22.2 ml/min) and II (mean -12.5 ml/min). The division in quartiles of ages showed an underestimation of GFR only in the first quartile of age (< 50 years old). Gates method underestimation of GFR was more pronounced in stage I patients treated with RAS inhibitors (mean -34.6 ml/min). The same occurs in stage II, even though to a lesser extent. ***Conclusion:*** The assessment of GFR by the Gates method must be carefully considered in the early stages of CKD, especially in younger patients. Moreover, the difference is more pronounced in patients treated with RAS inhibitors. Longitudinal studies will prove which method better predicts cardiovascular or renal events.

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Introduction

The incidence of chronic kidney disease (CKD) continues to increase worldwide. It is crucial in clinical practice to precisely define the level of renal impairment in order to properly stratify, establish therapeutic interventions, and predict outcomes of patients with CKD [1]. Inulin clearance represents the gold standard for GFR determination; however, it can not be applied widely because of its technical complexity and time-consuming procedure. The most common methods of assessment of kidney function are the estimation of the glomerular filtration rate (eGFR), calculated from the level of serum creatinine, and that of the measured clearance of creatinine (C_{CR}) from a 24-hour urine collection. Measurement of the C_{CR} is compromised by the tubular secretion of serum creatinine and tends to overestimate the GFR, especially at elevated serum creatinine levels [2]. As a result, the Cockroft-Gault formula to assess kidney function [3] was developed in 1976, and subsequently was replaced in the late 1990s by an equation to calculate the eGFR, derived from the Modification of Diet in Renal Disease (MDRD) Study on the effect of low-protein diet in CKD patients [4]. The CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula has been developed for the evaluation of kidney function in subjects with and without renal impairment, and has been demonstrated to be more accurate than the MDRD equation across most subgroups, especially for those with an eGFR of ≥ 60 mL/min/1.73 m^2 [5-6]. More recently, the Berlin Initiative Study Equation, performed both with cystatin or in alternative with creatinine, has been validated to estimate GFR in older patients with normal or mildly to moderately reduced kidney function [7].

Alternative methods for estimating renal function are the clearance of radioisotopes (plasma and/or urinary clearances of 14C-inulin, 51Cr-EDTA, 125I-iothalamate, 169Yb-DTPA, 99mTc-DTPA) or radiological contrast agents, as ioexhol. Dynamic renal scintigraphy is a radiologic procedure that takes advantage of the feature of selected radio-tracers, such as ^{99m}Tc-Diethylene Triamine Pentaacetic Acid (DTPA), to be eliminated by the kidneys in a way that is proportional to the level of renal function, which allows it to assess the level of kidney function as well as that of the urinary outflow. It is a simple and quick procedure that provides accurate information about the GFR, and where available is used regularly in hospital settings. However, as well as in other centers, we use it in our hospital for differential diagnosis between renal artery stenosis and essential hypertension (by using captopril) and between organic and functional obstructive uropathy (by using furosemide) [8].

The aim of the present study is to compare the accuracy and reliability of renal scintigraphy and eGFR estimated from the various formulas used in evaluating CKD patients and to identify variables associated in observed differences.

Patients and Methods

Study population

We retrospectively reviewed the records of 341 patients who underwent dynamic renal scintigraphy in the last 5 years of hospitalization in the Nephrology and Dialysis Unit of University of Messina. Kidney function was evaluated from the simultaneous assessment of eGFR calculated using the CKD-EPI formula, 4-variable MDRD Study equation, and renal scintigraphy with ^{99m}Tc-DTPA. Patients were categorized according to the Kidney Disease Improving Global Outcomes (KDIGO) stages of CKD using their eGFR level estimated by CKD-EPI formula.

We also stratified patients according to their treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), started at least three months before.

Serum creatinine levels were obtained from the routine laboratory database. No permission was required by our institutional Ethics Committee as the database was considered fully anonymous and no personal information was collected for this study. Serum creatinine was measured using an enzymatic technique (modular P Analyzer, creatinine plus assay; Roche Diagnostics, Mannheim, Germany).

GFR estimation

MDRD formula. Glomerular filtration rate was estimated by using the re-expressed 4-variable MDRD Study equation (GFR = 175 X standardized Scr $^{-1.154}$

X age $^{-0.203}$ X 1.212 [if black] X 0.742 [if female]) [4].

CKD-EPI equation. CKD-EPI equation, expressed as a single equation, is: GFR = 141 × min(Scr/κ, 1)$^{\alpha}$ × max(Scr/κ, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 [if female] _ 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1 [5-6].

Dynamic Renal Scintigraphy

Dynamic renal scintigraphy was performed by the intravenous injection of ^{99m}Tc-DTPA

(111 MBq). Thirty minutes before the start of the study, patients ingested 700 ml of water to achieve adequate hydration. The study was obtained using dual-headed gamma camera equipped with low-energy high-resolution parallel-hole collimator (LEHRPAR) peaked at 140 KeV energy peak ± 20% of energy window, with the patient in supine position over the detection head of the gamma-camera. Planar dynamic images (magnification: 1; matrix 256x256), obtained from posterior projection of the upper abdomen region (renal beds), were acquired 1 second per frame for the first minute (renal perfusion phase) and 15 seconds per frame (4 frames per minute) for the remaining study (parenchymal and excretion phases, respectively).

Images were processed by an Entegra (GE Medical System) workstation and regions of interest (ROI) were created around kidneys, near the organs (for the subtraction of the background activity) and around the aortic vessel (9). The values of GFR were calculated by the Gates method.

Statistical analysis

The numerical data are expressed as medians and ranges (minimum and maximum) and the categorical variables as numbers and percentages. Examined variables did not show a normal distribution as verified by the Kolmogorov-Smirnov test; consequently, the nonparametric approach has been used.

The Jonckheere–Terstra test was performed in order to assess the existence of a decreasing order of GFR in the different stages of CKD. The Jonckheere-Terpstra test was applied in place of the Kruskal-Wallis test, because it allows to assess an ordered alternative hypothesis. The Mann-Whitney test was used for each parameter of interest (GFR and Δ, namely the difference between eGFR calculated with the CKD-EPI formula and GFR determined through the Gates method), in order to perform the nonparametric comparison between patients treated (RAS 1) or not treated (RAS 0) with RAS inhibitors. Adequate bar graphs were realized in order to describe GFR and the trend of Δ within the different stages of eGFR, both for the whole sample and for patients receiving RAS inhibitors or not.

The Kruskall Wallis test was used to assess, for each parameter of interest, the existence of any significant difference among four age classes, identified by quartiles of the distribution; subsequently, the two-by-two comparisons between consecutive classes were performed by means of Mann Whitney test.

Statistical analyses were performed using SPSS 11.0 software for Window package. $P < 0.05$ was considered to be statistically significant.

Results

Subjects were stratified according to eGFR computed using the MDRD and CKD-EPI equation. Table 1 shows the clinical characteristics of subjects studied. Briefly, patients were distributed equally in all CKD stages (stage 1 17,3%, stage 2 19,4%, stage 3a 10,6%, stage 3b 15,2%, stage 4 19, 1%, stage 5 5,3%). The median age was 61.20 years ± 16.92 SD and 52.4% of the subjects were over 65 years. Diabetes mellitus was present in 24.9%, hypertension in 65.7% and 58,4% of the subjects were treated with RAS inhibitors.

When the subjects were divided in quartiles according to age, a distinct decrease in eGFR was evident with ageing. Indeed we have a mean of eGFR equal to 80,27 ml/min in the first quartile (<50 years old), whilst the last quartile (>75 years old) mean of eGFR was 36,26 ml/min (Table 2).

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Table 1. Characteristics of study subjects (n=341) and represented stages of CKD according to eGFR calculated using the CKD-EPI formula. (values are given as no. (%) or mean +/- SD.)

Group	Total	CKD stages						p-value
		1	2	3a	3b	4	5	
Patients	296 (86,8)	59 (17,3)	66 (19,4)	36 (10,6)	52 (15,2)	65 (19,1)	18 (5,3)	
Sex								0,029
Female	163 (47,8)	40 (67,8)	26 (39,4)	18 (50)	26 (50)	28 (43,1)	7 (38,9)	
Male	178 (52,2)	19 (32,2)	40 (60,6)	18 (50)	26 (50)	37 (56,9)	11 (61,1)	
Age (years) and SD	61,20 ±16,92	46,83 ±15,06	59,95 ±13,94	66,75 ±12,9	70,34 ±11,55	68,29 ±13,16	73,4 ±13,5	0,000
Diabetes Mellitus	85 (24,9)	10 (16,9)	17 (25,8)	13 (36,1)	10 (19,2)	22 (33,8)	7 (38,9)	0,106
Hypertension	224 (65,7)	34 (57,6)	46 (69,7)	26 (72,2)	39 (75)	46 (70,8)	14 (77,8)	0,339
Kidney Stones	29 (8,5)	9 (15,3)	8 (12,1)	3 (8,3)	4 (7,7)	1 (1,5)	1 (5,6)	0,127
Polycystic Kidney Disease	13 (3,8)	4 (6,8)	4 (6,1)	1 (2,8)	1 (1,9)	2 (3,1)	0 (0)	0,625
eGFR (mean) in No RAS Inhibition Therapy (RAS0)	199 (58,4)	90,48	63,08	54,69	35,75	31,56	21,12	0,000
eGFR (mean) in RAS Inhibition Therapy (RAS1)	142 (41,6)	70,4	57,3	43,2	38,1	26,2	10,5	0,000

Table 2. Study subjects (n=341): Creatinine clearance methods divided for quartiles of ages, (values are given as no. (%) or mean +/- SD.) and comparison between the different classes of ages. (°Kruskal-Wallis test)

Quartiles (age)	Patients n°	eGFR (CKD-EPI)	eGFR (MDRD)	eGFR (Gates Method)	Difference CKD-EPI vs Gates Method
<50	89	80,27 ml/min ±39,04	77,34 ml/min ±47,04	78,69 ml/min ±32,64	17,39 ml/min ±53,90
51-65	93	63,6 ml/min ±28,7	61,30 ml/min ±28,89	59,58 ml/min ±25,83	0,80 ml/min ±30,40
66-74	84	45,28 ml/min ±24,7	44,52 ml/min ±26,60	38,45 ml/min ±17,59	-3,77 ml/min ±24,91
>75	75	36,26 ml/min ±20,32	37,84 ml/min ±21,49	33,17 ml/min ±18,05	-1,27 ml/min ±16,09
			Comparison between the different classes of ages°		
All groups	341	0,000	0,000	0,000	0,136

As shown in Figure 1 there was no significant difference within the KDIGO stages 1 to 5, of the eGFR levels calculated by the MDRD and CKD-EPI equations. However, the levels of GFR determined by the Gates method were different in all 5 stages of CKD classified according to the CKD-EPI formula (JT statistic = -14.89, p = 0.000). The Gates method tended to underestimate the eGFR assessed with the CKD-EPI formula in CKD stages-I (mean value -22.2 ml/min) and II (mean value -12.5 ml/min), whereas it was likely to overestimate it in stages-IV (average value +5.8 ml/min) and V (average value +3.8 ml/min) [Figure 2]. The best agreement between Gates method and CKD-EPI formula was observed in stage 3b (mean value -0,2 ml/min), whilst in stage 3a the Gates method tended to slightly underestimate the eGFR (mean value - 4.6 ml/min). The Jonckheere-Terpstra test also revealed that there is a significantly increasing trend of Δ value through the different clearance stages (JT statistic = 8.364, p = 0.000). Compared to the CKD-EPI formula, using the MDRD equation seems to underestimate more strongly the Gates levels especially for CKD stage 1 [Figure 2].

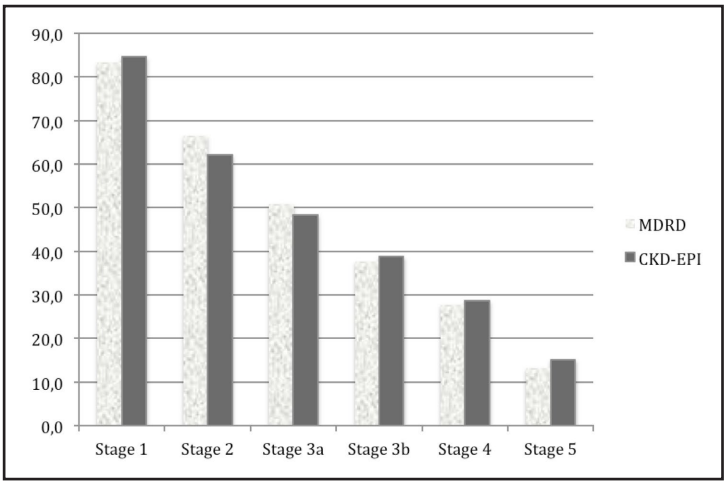

Fig. 1. Mean eGFR levels calculated by the MDRD and CKD-EPI within the KDIGO staging of stuided sublects (n=341).

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DOI: 10.1159/000355813
Published online: December 19, 2014

Statistically significant differences were found in patients on RAS-inhibitors (RAS 1) compared to those not receiving these medications (RAS 0). In particular, using the Gates method, the understimation of the GFR tends to become even more pronounced with respect to the eGFR evaluated with the CKD-EPI formula in stage I patients who are treated (RAS 1: average value -34.6 ml/min) (Figure 3) versus patients not on therapy (RAS 0: average value -17.1 ml/min) (Figure 4). The same occurs in stage II, even though to a lesser extent. In stages IV and V, Gates method overestimated GFR evaluated with CKD-EPI formula in patients treated with RAS-inhibitors. Moreover, there was a significantly decreasing trend of GFR values calculated with the Gates method in the various CKD stages (JT statistic = 9.879, p = 0.000) for the latter group of patients. Finally, a significant increase in trend of Δ values in the different clearance stages (JT statistic = 6.244, p = 0.000) was detected. Moreover, the difference between CKD-EPI and Gates Method in the lower group of age (<50 yrs) was enhanced by the contemporary use of ACEI or ARBs.

Discussion

Our study demonstrates that in the various stages of CKD there are significant differences in the assessment of renal func-

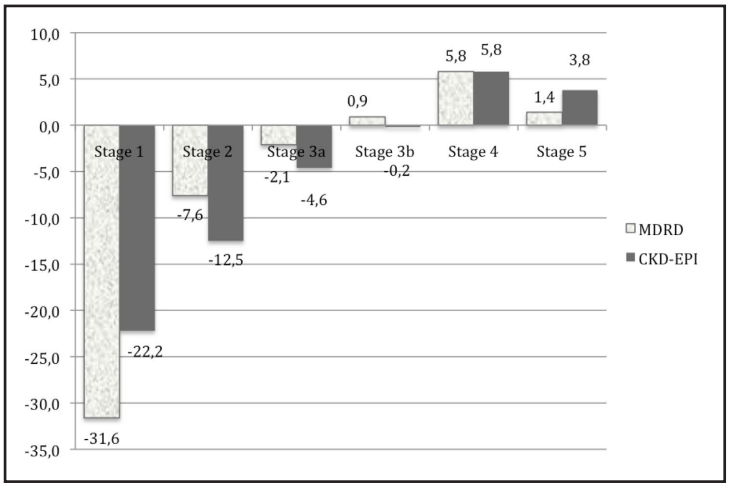

Fig. 2. Difference between eGFR according to the MDRD and CKD-EPI formulas and that obtained with renal scintigraphy in the different KDIGO stages.

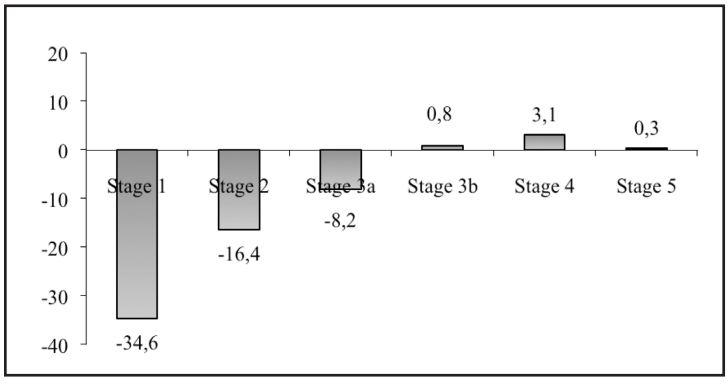

Fig. 3. Patients (n=142) **treated** with RAS inhibitors (**RAS 1**): Δ between eGFR according to CKD-EPI formula and GFR obtained with renal scintigraphy (calculated by Gates method).

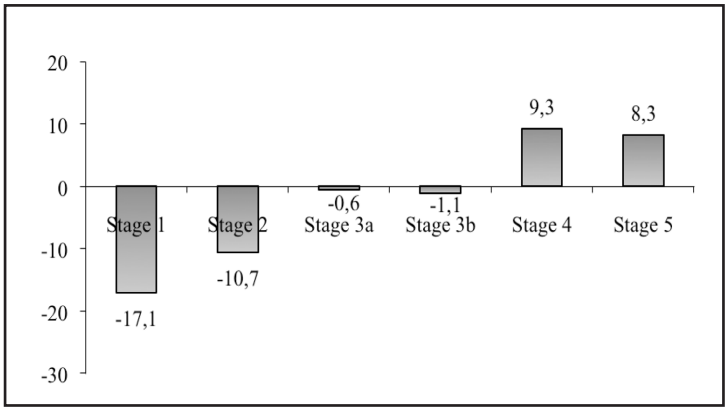

Fig. 4. Patients (n°199) **not treated** with RAS inhibitors (**RAS 0**): Δ between eGFR according to CKD-EPI formula and GFR obtained with renal scintigraphy (calculated by Gates method).

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DOI: 10.1159/000355813
Published online: December 19, 2014

tion between eGFR calculated using both the CKD-EPI and MDRD formulas and GFR determined by the Gates method at renal scintigraphy. In particular, compared to the CKD-EPI formula, the Gates method tends to underestimate the GFR in CKD stages I and II, and in contrast overestimates it in stages IV and V.

Accurate staging of CKD is essential for the proper management of the kidney patients. Indeed in clinical practice, especially in the elderly, the presence of discrepancies in the GFR value when different methods are used to determine it can be confusing, resulting in errors of judgment that may adversely affect the appropriateness of treatment, and whether further diagnostic procedures or therapeutic approaches are undertaken [10-11].

When MDRD and CKD-EPI equations were developed, plasma clearance of iothalamate was used as reference standard. CKD-EPI equation performed better than MDRD equation for the difference between estimated and measured GFR (7).

Dynamic renal scintigraphy is a sensitive, rapid and non-invasive technique to quantify renal function and urodynamics. This procedure employs tracers that are not nephrotoxic, unlike iodinated contrast media employed in radiology [12]. In addition, it allows to separately evaluate the function of the two kidneys: this opportunity is very important when there is a condition of asymmetric renal hypofunction (congenital abnormalities, pyelonephritis, vesicoureteral reflux, obstructive nephropathy, vascular disorders, space-occupying lesions, post-traumatic alterations) or when it is necessary to consider a surgical procedure [13]. Lastly, a recent study has shown that ^{99m}Tc-DTPA renal scintigraphy is able to predict the overall cardiovascular risk in hypertensive patients with normal serum creatinine values [14].

Gates method is designed to approximate 24-hour creatinine clearance, that Gates used as reference standard [15].

However, the use of renal scintigraphy in the evaluation of kidney function is a highly expensive method and is difficult to be extended in the nephrological routine; therefore, it is normally performed only in selected cases. Furthermore, in most of the clinical trials carried out in the population of CKD patients, the use of a simple formula that estimates renal function using only serum creatinine value is extremely helpful and has a well-established efficacy [16-18]. Another practical advantage resulting from the use of formulas is the possibility to calculate a reliable value of renal function in the so-called "not nephrological" areas that host a large number of patients with renal disease, such as some hospital wards (cardiology, internal medicine, etc), specialist outpatient clinics for internal diseases (diabetes mellitus, arterial hypertension, dyslipidemia) or even the offices of primary care physicians. In all the mentioned areas, the eGFR evaluation would definitely increase the number of patients that could be early referred to nephrologists.

Since in our cohort of patients we found a different GFR between renal scintigraphy and the estimated formula, one of the problems that needs to be solved is what importance we should give to two different values for the definition of CKD stages. Assuming that scintigraphy is supposed to represent the gold standard by some authors [19], one could say that the CKD-EPI formula tends to overestimate the GFR obtained through renal scintigraphy in CKD stages I and II and to underestimate it in stages IV and V.

On the contrary, we decided to consider the CKD-EPI formula as the reference GFR, and to compare it with that one obtained with scintigraphy. To confirm our choice, there were some data about the greater plausibility of the results obtained with the estimated formula with respect to renal scintigraphy. In particular, we mention the case of a 27-year-old woman whose serum creatinine value was 0.7 mg/dl and whose eGFR was 119 ml/min whereas the same value assessed by renal scintigraphy was 35 ml/min. Although this can be considered an extreme comparison, the fact that renal scintigraphy may underestimate eGFR of 22 ml/min on average at CKD stage I reinforces the concept of the greater plausibility of the CKD-EPI formula as reference GFR. Of course, our study is cross-sectional and can only provide a static picture of the differences between the two methods. A longitudinal evaluation will probably establish, in terms of progression of renal disease or overall cardiovascular risk [14], which of the two values could represent a more predictable marker.

However in other studies, nuclear medicine methods showed to overestimate instead of underestimate GFR. Since creatinine clearance overestimates true GFR (because of tubular secretion of this substance), results obtained with Gates method cannot be equal to those obtained by the equations designed to match true GFR (MDRD and CKD-EPI). Therefore, Gates method, as creatinine clearance, should overestimate the true GFR, and this finding has been repeatedly reported. In particular, in a population of 115 potential kidney donors with normal renal function the Gates method overestimated GFR [20]. Moreover, a recent comparison between 99mTc-DTPA clearance using the Gates method and a two-blood sample method with MDRD and CKD-EPI, in a population of renal donor candidates and oncological patients treated with nephrotoxic chemotherapy, showed that nuclear medicine methods overestimated the GFR value in comparison to creatinine based equations [21]. The authors suggested that nuclear methods are unavailable due to cost or accessibility issues, eGFR with CKD-EPI appears to reflect renal function more accurately than MDRD, and thus should be the method of choice for estimating GFR.

Differently from what above reported, we obtained different values for renal filtration with higher values for eGFR (MDRD and CKD-EPI) and in the same patients lower GFR when Gates method was used to estimate renal function, especially in the early stages (I and II) of CKD.

The division of patients in classes of ages (quartiles) to explore any influence of age in staging and difference between methods resulted in two interesting findings. First of all, we found that older patients were characterized by lower levels of eGFR. Considering that with advancing age there is a progressive decline in renal function, we can conclude that in our population the difference in terms of renal function are due to ageing rather than different renal disease. Moreover, we found that the difference between eGFR evaluated with CKD-EPI formula and Gates method are evident only in patients in the first class of age (<50 years old).

Lastly, in order to examine variables that could influence the differences in GFR values obtained with the two methods, we evaluated the use of drugs that act on the renin-angiotensin system [22], that is able to modify the GFR through variations in haemodynamic mechanisms of renal physiology.

We observed that treatment with RAS-inhibitors is able to further accentuate the underestimation of the GFR obtained with the renal scintigraphy compared with the CKD-EPI formula in CKD stages I and II.

Starting from the assumption that the use of a drug active on the RAS causes a slight increase in the serum creatinine value and that this rise consequently alters the eGFR, it must be supposed that the haemodynamic alteration induced by these medications is even more important in the determination of the final GFR value obtained with the scintigraphic method. After all, captopril renal scintigraphy is used when a renal artery stenosis is suspected precisely because in the ischemic kidney both GFR and the renal plasma flow depend on the efferent arteriolar vasoconstriction mediated by angiotensin II, and the blockade of such vasoconstriction due to the administration of the ACE inhibitor induces a decline in GFR in the stenotic kidney [23].

Whilst renal scintigraphy is not always a valid method to assess GFR in the early stages of CKD, eGFR evaluated with CKD-EPI has been validated for patients with eGFR>or=60 mL/min/1.73 m2 (5). Moreover, the difference between the two methods is increased by the use of drugs that act on RAS, suggesting also an haemodynamic component.

Conclusion

The assessment of GFR by the Gates method must be carefully evaluated in the early stages of CKD, when the risk of an underestimation seems to be greater. This underestimation is more evident for patients less that 50 years old. This measurement proves to be more

appropriate in stage III, when the degree of such differences is lesser. Besides, drugs that act on the RAS make the difference even more pronounced. Longitudinal studies will enable us to understand which of these two parameters better allow to predict cardiovascular or renal events.

Disclosure Statement

The authors of this manuscript state that they do not have any conflict of interests and nothing to disclose.

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