The estimation of glomerular filtration rate in type 2 diabetic patients may depend on the equation used

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Abstract. – BACKGROUND: The aim of this study was to compare the estimation of glomerular filtration rate (GFR) in type 2 diabetes mellitus (DM) outpatients.

PATIENTS AND METHODS: The study included 1686 subjects, aged 68±10 years. GFR was evaluated with five different equations: GFRMDRD186, GFRMDRD175, GFRCKD-EPI, GFR-MAYO, GFRC-G.

RESULTS: GFR was lower than 60 ml min^{-1} kg^{-1} in 456 patients (27%) by GFRMDRD186, in 531 (31.5%) by GFRMDRD175, in 504 (30%) by GFRCKD-EPI, in 433 (26%) by GFRC-G, and in 255 (15%) by GFRMAYO. The mean differences in measuring GFR with the different formulae ranged from 1.03±6.20 to -14.5±11.9 ml min^{-1} 1.73 m$^{2-1}$.

CONCLUSIONS: The evaluation of GFR with different formulae in type 2 DM patients may identify different chronic kidney disease (CKD) stages. Physicians could take advantage by the knowledge of the formula used for evaluation of renal function, for a better interpretation of values and a more appropriate use in the everyday clinical practice.

Key Words:
 Diabetes Mellitus, Type 2, Chronic kidney disease Kidney failure, Glomerular filtration rate, Equations.

Introduction

Early diagnosis of chronic kidney disease (CKD) is essential in patients with diabetes mellitus (DM), in order to identify subjects at risk of adverse outcome. Current clinical practice suggests an yearly evaluation of the glomerular filtration rate (GFR). A recent study conducted in the United States[1], aimed to evaluate the 10 year risk of total cardiovascular disease (CVD) by the use of global risk assessment equations, found that many DM patients were not at high 10 year CVD risk. However, renal disease, defined by GFR < 60 ml/min^{-1} 1.73 m$^{2-1}$, was higher in the high risk group and in subjects with pre-existing CVD and intermediate risk. Moreover, in DM patients, it is known that the monitoring of GFR with commonly accepted formulae cannot precisely define the slope of decreasing renal function[2].

The National Kidney Foundation guidelines for CKD recommend the assessment of renal function estimating the GFR by using validated equations. In adults, the modification of diet in renal disease (MDRD) study and Cockcroft-Gault (CG) equations are the most popular[3-5]. Besides a new quadratic equation has been introduced in clinical practice in order to overcome the underestimation of GFR in healthy persons by MDRD equation[6]. Furthermore, the CKD-EPI equation was developed in order to ameliorate the performance of formulae in detecting CKD[7].

Since the evaluation of renal function could be essential for determining CVD risk in DM, the aim of this study was the comparison of different equations in estimating GFR in the real world of daily clinical practice in a cohort od type 2 DM outpatients.

Patients and Methods

This cross-sectional study, performed under the terms of the Declaration of Helsinki as revised in 2000, included a cohort of Caucasian type 2 DM outpatients consecutively observed at our Hospital's referral Centre between January 2009 and December 2009. Subjects treated with insulin and those on renal replacement therapy were excluded. Height and weight were measured during clinical assessment, and body mass index (BMI) was calculated as weight (kg)/ height (m^2). Blood samples for serum determination of creatinine, glucose, glycated haemoglobin

(Variant II HbA2/HbA1c Dual Program) were drawn in the morning after 12 hour fasting. Serum creatinine (SCr) levels assays were all performed with the Jaffe method on a Hitachi Modular (Roche Diagnostics, Mannheim, Germany). Office blood pressure (BP) was measured with a mercury sphygmomanometer under standardised conditions (between 09:00 and 11:00 after 10 minutes rest in the sitting position: no meal, no alcohol or caffeine ingestion in the 2 preceding hours). Averages from at least three measurements taken during three different visits were calculated. For each patient, renal function was evaluated by estimated glomerular filtration rate (eGFR) using the following equations (SCr = serum creatinine):

Modification of Diet in Renal Disease (MDRD)$_{186}$ formula[3]: $GFR_{MDRD186} = 186 \times (SCr)^{-1.154} \times [age(years)]^{-0.203} \times (0.742$ if female$) \times (1.212$ if African-American$)$

MDRD$_{175}$ formula[8]: $GFR_{MDRD175} = 175 \times (SCr)^{-1.154} \times [age \ (years)]^{-0.203} \times (0.742$ if female$) \times (1.212$ if African-American$)$

Mayo Clinic Quadratic formula[6]: $GFR_{MAYO} = \exp[1.911 + 5.249/SCr - 2.114/SCr^2 - 0.00686 \times age (years) - 0.205$ (if female)$]$

Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula[7]:
– If female and if SCr ≤ 0.7 mg/dl:
$GFR_{CDK-EPI} = 144 \times SCr/0.7^{-0.329} \times 0.993^{age}$
– If female and if SCr > 0.7 mg/dl:
$GFR_{CDK-EPI} = 144 \times SCr/0.7^{-1.209} \times 0.993^{age}$
– If male and if SCr ≤ 0.9 mg/dl:
$GFR_{CDK-EPI} = 141 \times SCr/0.9^{-0.411} \times 0.993^{age}$
– If male and if SCr > 0.9 mg/dl:
$GFR \ CDK-EPI = 141 \times SCr/0.9^{-1.209} \times 0.993^{age}$
Cockcroft-Gault formula[4]:
$CrCl_{C-G} = [140-age \ (years)] \times$ body weight (kg)$/72 \times SCr$ (mg/dl) ($\times 0.85$ if female)

Statistical Analysis

Data were expressed as mean ± SD or as percentage. One-way ANOVA was used to compare parametric continuous variables.

GFR calculated by different equations was tested with Pearson's correlation coefficient calculation. Values derived from the three formulae were compared by Bland-Altman analysis[9] $GFR_{MDRD186}$ and $GFR_{MDRD175}$ were not compared because the only difference in the two equations was the constant.

Statistical significance was defined as $p < 0.05$. Statview for Windows (version 3.0, SAS Institute Inc. San Francisco, CA, USA) was used for the calculations.

Results

The study included 1686 type 2 DM patients (57.1% males), mean age of 68±10 years, mean BMI was 30±5 kg/m^2, mean systolic and diastolic BP 138±15 and 80±9 mmHg, respectively. As for their therapeutic regimen, 117 (7%) were on glitazones, 665 (39.5%) on metformin, 114 (6.8%) on repaglinide, 178 (10.5%) on sulphonylureas, 600 (35.5%) on sulphonylureas and metformin, and 12 (0.7%) on dipeptidyl peptidase 4 (dpp4) inhibitors. Laboratory examinations showed mean fasting glucose level 114±51 mg/dl, glycated haemoglobin 8±1%, serum creatinine 1.03±0.35 mg/dl.

The whole population showed a better renal function when it was evaluated with Mayo and Cockcroft-Gault formulae, and a worse renal function when it was calculated with $GFR_{MDRD175}$ formula. Serum creatinine was equal or lower than 1.22 mg/dl in 1371 subjects (81%). GFR was lower than 60 ml min^{-1} 1.73 m$^{2-1}$ in 456 patients (27%) by $GFR_{MDRD186}$, in 531 (31.5%) by

Table I. Mean ± standard deviation (SD) values of GFR estimated with different equations, and percentage of subjects with GFR lower than 60 ml min^{-1} 1.73 m$^{2-1}$. $CrCl_{C-G}$ and GFR_{MAYO} show similar values, whereas the mean values derived from other equations are statistically different ($p < 0.0001$).

	Mean value (ml min^{-1} 1.73 m$^{2-1}$)	Range (ml min^{-1} 1.73 m$^{2-1}$)	Percentage of subjects with GFR < 60 ml min^{-1} 1.73 m$^{2-1}$
$GFR_{CKD-EPI}$	71.2 ± 21.1	11.5-126.7	30% (n = 504)
$GFR_{MDRD186}$	74.7 ± 23.5	13.5-175.5	27% (n = 456)
$GFR_{MDRD175}$	70.1 ± 22.1	12.7-164.9	31.5% (n = 531)
$CrCl_{C-G}$	84.4 ± 36.4	13.1-279.3	26% (n = 433)
GFR_{MAYO}	84.7 ± 22.6	11.3-142.1	15% (n = 255)

Table II. Pearson's coefficient between different values of GFR calculated with the different formulae.

	GFR$_{CKD-EPI}$	GFR$_{MDRD186}$	GFR$_{MDRD175}$	CrCl$_{C-G}$	GFR$_{MAYO}$
GFR$_{CKD-EPI}$	1	0.960 ($p < 0.0001$)	0.960 ($p < 0.0001$)	0.819 ($p < 0.0001$)	0.932 ($p < 0.0001$)
GFR$_{MDRD186}$	0.960 ($p < 0.0001$)	1	0.960 ($p < 0.0001$)	0.791 ($p < 0.0001$)	0.858 ($p < 0.0001$)
GFR$_{MDRD175}$	0.960 ($p < 0.0001$)	0.960 ($p < 0.0001$)	1	0.791 ($p < 0.0001$)	0.858 ($p < 0.0001$)
CrCl$_{C-G}$	0.819 ($p < 0.0001$)	0.791 ($p < 0.0001$)	0.791 ($p < 0.0001$)	1	0.752 ($p < 0.0001$)
GFR$_{MAYO}$	0.932 ($p < 0.0001$)	0.858 ($p < 0.0001$)	0.858 ($p < 0.0001$)	0.752 ($p < 0.0001$)	1

GFR$_{MDRD175}$, in 504 (30%) by GFR$_{CKD-EPI}$, in 433 (26%) by GFR$_{C-G}$, and in 255 (15%) by GFR$_{MAYO}$ (Table I).

The results obtained from the five formulae were highly correlated (Table II). Mean, standard deviation of differences, interquartile range, minimum and maximum of differences in measuring GFR with the five different equations are reported in Table III. Bland-Altman analysis confirmed that the results of the five formulae were not in agreement, since the plots were distant from the zero line, especially in the case of high GFR (Figure 1).

Discussion

Chronic kidney disease is often associated with type 2 DM. Data from the fourth National Health and Nutrition Examination Survey (NHANES-IV, 1999-2004) found that nearly 40% of adult patients with type 2 DM had a certain degree of CKD[10]. Diabetes is the major risk factor for development of kidney disease, and it has been reported that 20 to 40% of diabetics develop renal damage, as shown by recent laboratory methods[11]. In Italy, diabetes is the cause of end-stage renal disease (ESRD) in 19.6% of incident dialysis patients, the prevalence of diabetic nephropathy has recently increased[12], and up to 40% of diabetic subjects develop diabetic nephropathy[13]. Precise estimation of GFR is crucial for diagnosing and evaluating CKD, since underestimation or overestimation of GFR could result in unnecessary or missing investigation and interventions in type 2 DM patients. Indeed, the underestimation of CKD was common before the development of five-stage classification system for CKD worked out by the National Center for Health Statistics[14]. Early recognition of CKD is essential in order to avoid adverse outcomes of CKD. The association of early stage of CKD with different co-morbidity could represent a cause of under-recognition[15]. Therefore, estimation of GFR from serum creatinine, age, sex, race and body size is recommended. Creatinine, however, is a useful marker of GFR in steady state only, but if acute renal failure is present it does not accurately reflect the real GFR. Moreover, the different formulas do not appear to fit in the same way each group of different patients.

The American Diabetes Association suggests to estimate GFR from serum creatinine using the MDRD equation[16]. However, it has been reported

Table III. Mean, 2 standard deviation (2SD), interquartile range (IQR), minimum and maximum of differences in measuring GFR with the different equations.

	Mean	2SD	IQR	Minimum	Maximum
GFR$_{CKD-EPI}$-GFR$_{MDRD175}$	1.03	12.40	5.09	-55.48	16.33
GFR$_{CKD-EPI}$-GFR$_{MDRD186}$	-3.49	13.52	4.27	-66.01	10.32
GFR$_{CKD-EPI}$-CrCl$_{C-G}$	-13.26	45.34	22.68	-159.52	43.02
GFR$_{CKD-EPI}$-GFR$_{MAYO}$	-13.54	16.36	9.88	-30.69	16.62
GFR$_{MDRD175}$-CrCl$_{C-G}$	-14.29	46.58	25.43	-143.98	52.73
GFR$_{MDRD175}$-GFR$_{MAYO}$	-14.57	23.80	12.94	-36.99	70.17
GFR$_{MDRD186}$-CrCl$_{C-G}$	-9.76	45.82	24.46	-135.88	58.69
GFR$_{MDRD186}$-GFR$_{MAYO}$	-10.00	24.60	12.76	-30.82	80.20
CrCl$_{C-G}$-GFR$_{MAYO}$	-0.28	49.00	24.21	-59.87	171.94
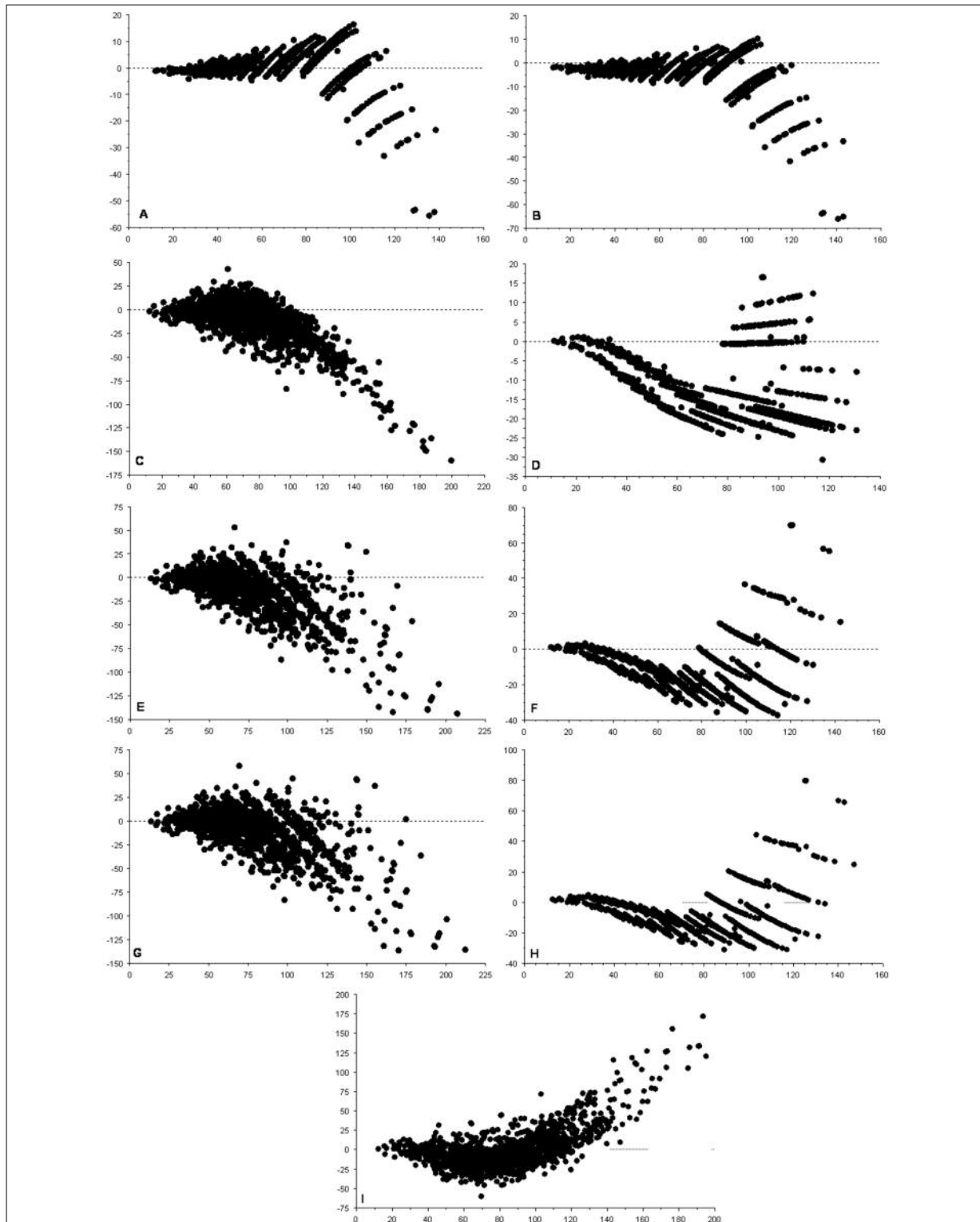
Figure 1. Bland-Altman analysis: **A,** Between $GFR_{CKD-EPI}$-$GFR_{MDRD175}$ (Y) and ($GFR_{CKD-EPI}$ + $GFR_{MDRD175}$)/2 (X); **B,** Between $GFR_{CKD-EPI}$-$GFR_{MDRD186}$ (Y) and ($GFR_{CKD-EPI}$ + $GFR_{MDRD186}$)/2 (X); **C,** Between $GFR_{CKD-EPI}$-$CrCl_{C-G}$ (Y) and ($GFR_{CKD-EPI}$ + $CrCl_{C-G}$)/2 (X); **D,** Between $GFR_{CKD-EPI}$-GFR_{MAYO} (Y) and ($GFR_{CKD-EPI}$ + GFR_{MAYO})/2 (X); **E,** Between $GFR_{MDRD175}$-$CrCl_{C-G}$ (Y) and ($GFR_{MDRD175}$ + $CrCl_{C-G}$)/2 (X); **F,** Between $GFR_{MDRD175}$-GFR_{MAYO} (Y) and ($GFR_{MDRD175}$ +GFR_{MAYO})/2 (X); **G,** Between $GFR_{MDRD186}$-$CrCl_{C-G}$ (Y) and ($GFR_{MDRD186}$ + $CrCl_{C-G}$)/2 (X); **H,** Between $GFR_{MDRD186}$-GFR_{MAYO} (Y) and ($GFR_{MDRD186}$ + GFR_{MAYO})/2 (X); **I,** Between $CrCl_{C-G}$-GFR_{MAYO} (Y) and ($CrCl_{C-G}$ + GFR_{MAYO})/2 (X).

that MDRD equation may underestimate GFR in type 2 DM patients with normal and high GFR[17], and may be inaccurate in normoalbuminuric diabetic patients[18]. Although evaluation of GFR is crucial for CKD diagnosis and staging, different creatinine based GFR estimating equations may misclassify type 2 DM patients. The increasing prevalence of CKD is probably due both to the improving of therapies and to an earlier diagnosis of diabetes and its related conditions. The development of equations to calculate GFR gave crucial support not only to early identify CKD, but also to monitor its progression. A recent study on 15,773 patients with type 2 DM, evaluated the burden of CVD associated with CKD diagnosed using CKD-EPI and MDRD equations[19]. The Authors found that prevalence of CKD was lower using CKD-EPI than MDRD formula. Indeed, the subjects with CKD assessed by MDRD had both lower CVD prevalence and coronary disease risk score. In particular, this score was mainly driven by female sex, younger age and shorter diabetes disturbs as compared with patients assessed by both of equations. Opposite results were demonstrated in subjects with CKD diagnosed with CKD-EPI formula[19]. The use of Cockroft-Gault formula is suggested by pharmacokinetic studies for guiding drug dosing in diabetic patients[20]. The National Kidney Disease Education Program recommends that either the MDRD study equation or Cockcroft-Gault can be used to estimate kidney function for drug dosing[21]. Stevens et al[22] showed that there was a concordance rate of 89% for kidney function estimates derived for Cockcroft-Gault and for the assignment of kidney function categories for drug dosing adjustment.

The guidelines for treatment of hyperglycemia do not consider renal function, and efficacy and safety of different agents in cases of reduced renal function should be acknowledged in order to ensure the best therapy. Our data, referring to a large cohort of diabetic outpatients, give further confirmation that estimation of GFR is inaccurate in population without known CKD[23]. The sensitivity of Cockroft-Gault and MDRD equations in diagnosing CKD is lower when GFR is higher than 60 ml/min/1.73[24] m². The MDRD equation was developed in established out CKD patients using 125-iothalomate renal clearance as a reference. The sample upon which the MDRD is based excluded patients with diabetic kidney disease or people aged 70 years and older. The MDRD study equation was derived from primarily white patients aged 51±12 affected by non-diabetic kidney disease with mean GFR of 40 ml min^{-1} 1.73 m$^{2-1}$. The CKD-EPI equation was developed to provide a more accurate estimate of renal function among subjects with GFR above 60 ml/min^{-1} 1.73 m$^{2-1}$ including populations with and without kidney disease[7]. Therefore, prevalence of CKD should be lower if CKD-EPI equation is calculated to define CKD. Moreover, CKD-EPI equation could help in detecting CKD in subjects with high cardiovascular disease risk[7]. The estimated GFR best correlates with the true GFR in the population under original study. In CKD patients with measured GFR less than 60 ml/min^{-1} 1.73 m$^{2-1}$, the MDRD equation correlates well, although it has not been well validated in other patients population. For instance, it is not useful in persons with normal renal function and it was not validated in persons over 70 years of age, or in hospitalized patients or in malnourished patients. In renal transplant donors, both the MDRD and the CG equation significantly underestimate measured GFR as 9% to 29%[25]. The K/DOKI guidelines define CKD as an estimated GFR < 60 ml/min^{-1} 1.73 m$^{2-1}$ and separate CKD into five stages[5]. However, this is an imperfect system. CKD is a progressive disease with a variable rate of decline. A GFR of 30 ml/min^{-1} 1.73 m$^{2-1}$ has half of the renal function as a GFR of 60 ml/min^{-1} 1.73 m$^{2-1}$, even though they are classified as stage III CKD. A GFR of 29 ml/min^{-1} 1.73 m$^{2-1}$ has virtually the same renal function as a GFR of 30 ml/min^{-1} 1.73 m$^{2-1}$, even though one is classified as stage IV and the other is classified as stage III. A decline from a previous of 120 ml/min^{-1} 1.73 m$^{2-1}$ to 80 ml/min^{-1} 1.73 m$^{2-1}$ is a significant decline in renal function, even though it is not considered CKD.

In this study, we excluded DM patients treated with insulin because they are at particularly high CVD risk, and in Italy they are mostly treated by hospital diabetologist (whereas the majority of DM patients are in charge to their general practitioner). The exact evaluation of CVD risk appears to be more important at the initial stage of diabetes due to the need of an aggressive clinical management in order to prevent complications. The prevalence of subjects with CKD varies depending on the formula used for GFR calculation, and accuracy, precision and bias are very important points in any formula used to calculate GFR in order to diagnose and stage CKD. Altogether, it appears that the use of different equations for estimation of GFR could impact diagno-

sis of diabetic nephropathy, that is crucial to predict progression to uremia. Our results show that prevalence of renal insufficiency depends not only on the population characteristics but also on the equation used to estimate renal function. GFR estimation is clinically important to assess the degree of kidney dysfunction and to evaluate the course of the disease.

Our results clearly show that there is not concordance in calculating GFR by different equations especially in the presence of high GFR. Classification of subject as CKD or no-CKD patients by different equations means to assign a different risk of ESRD, all cause mortality, coronary artery disease, and stroke, with consequent different burden on social costs. At least to the best of our knowledge, this is the first study comparing the clinical performance of five equations for estimating GFR in a large cohort of type 2 DM outpatients. Nevertheless, this study has several limitations. First, a gold standard method for calculating GFR as a reference method is lacking. We did not collect 24 hour urine output; therefore, we could not calculate creatinine clearance, a semi-gold standard to evaluate kidney function, nor we estimated cystatin C, which is constantly produced and excreted by the kidney[26-27-28]. Second, the cross-sectional design could reduce the impact of our results, since we cannot say anything about renal function monitoring with the different equations. Third, the cardiovascular risk score of each patient was not assessed, and subjects who suffered a cardiovascular event could have a lower renal function than those who did not. However, our aim was merely to show how the different formulae work in a clinical setting. We believe that, in the real world of everyday clinical practice, physicians could take advantage by the knowledge of the method used for evaluation of renal function, and this information could greatly help the interpretation of different values. In fact, the choice of the formula in agreement with the final use may play a pivotal role. For example, if the aim is the management of drug therapy, pharmacokinetic studies recommend the use of Cockroft-Gault equation to estimate renal function. Moreover, if the purpose is to stage and monitor renal function, MDRD and CKD-EPI equations, depending on demographic characteristics of patients, could fit more appropriately. However, physicians (and general practitioners in particular) should be aware of the limitations of the different formulae at the time of office evaluation, since the slope of

the curve showing the decreasing GFR could be slightly different[2], and also the evaluation of clinical risk linked to reduced renal function could be different.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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