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Creatinine Clearance and Estimated Glomerular Filtration Rate – When are they Interchangeable

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ABSTRACT

Study goal was to examine which of glomerular rate equations is most suitable for prediction of creatinine clearance (CrCl). Using a retrospective review of data from 500 hospital patients we calculated glomerular filtration rate according to Cockcroft-Gault equation (C-G), Modification of Diet in Renal Disease Study equation (MDRD) and Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI). We determined if results of these equations were compatible with CrCl, and does stage of kidney disease, body-mass index (BMI), diabetes or old age have an impact on their ability to predict creatinine clearance. All of the equations showed high correlations with CrCl, regardless of diabetes, overweight or old age. There was no significant difference ($p<0.05$) between diagnostic accuracy when comparing ROC plots for MDRD and CKD-EPI at CrCl cut offs of 60 ml/min/1.73 m2 and 90 ml/min/1.73 m2 when analyzing data for all patients, older patients (>65 years) and diabetics. The percentage of overweight patients (BMI≥25) in patients with normal CrCl and decreased GFR was 64.81% for C-G, 92.04% for MDRD and 91.36% for CKD-EPI. Large number of overweight patients with normal CrCl and decreased GFR would indicate that CrCl overestimates GFR in overweight patients. The simple correction in CrCl for obese subjects is purposed. Passing-Bablok regression showed agreement between CrCl and MDRD and CrCl and CKD-EPI only in cases of severely decreased GFR (G4 and G5 stage of chronic kidney disease). Only in these stages of chronic kidney disease can CrCl and MDRD or CrCl and CKD-EPI be used simultaneously.

Key words: *creatinine clearance, Cockcroft-Gault equation, Modified Diet in Renal Disease equation, Chronic Kidney Disease Epidemiology Collaboration equation, chronic kidney disease, diabetes mellitus*

Introduction

According to the guidelines that were introduced by the Kidney Disease Outcomes Quality Initiative (KDOQI) chronic kidney disease (CKD) is a common condition defined by the presence of kidney damage or decreased kidney function for three or more months. Regardless what the cause may be, it requires early detection and management[1]. Monitoring of high risk patients, such as hypertonic, diabetic or overweight individuals is crucial in preventing kidney failure. Determining the glomerular filtration rate is the most reliable test to asses overall functional kidney capacity. Large studies produced equations, such as Cockcroft-Gault, MDRD and CKD-EPI equation for calculation of glomerular filtration rate[2,3]. These equations have not been tested in Croatian hospital population. In Croatia, the most widely used method of assessment of GFR is CrCl, a routine but not exact method. CrCl is an impractical aproximative method that is largely influenced by incorrect 24-hour urine collection. Another possible reason for CrCl variability is the fact that it uses urine creatinine concentration which is a result of glomerular filtration of creatinine but also secretion of creatinine in tubules (up to 7% of urinary creatinine is secreted by tubules). Thus, it was our goal to asses if there are any differences in CrCl and eGFR assessed glomerular filtration rate. If there was no difference between eGFR and CrCl, laboratories could use eGFR and CrCl simultaneosly in diagnostics of chronic kidney disease and increase the number of early diagnosed patients with decreased glomerular filtration. Preanalytical phase, which

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in case of determining creatinine clearance contains the collection of 24-hour urine, would be eliminated, since it is a demanding for patients and hospital staff. The cost of laboratory tests would be reduced by incorporating one of these equations because it would eliminate the need for determination of urine creatinine.

Determination of creatinine clearance has been shown to have many limitations. It is dependent on muscular mass and weight of patients, and it decreases with age. There is a big intra-individual variability in excretion of creatinine (up to 14%)[4]. Collection of timed 24-hour urine in which creatinine clearance is determined is uncontrolled and impractical for patients, since it is done more often in their homes instead in hospital conditions. So it often results in preanalytical errors. As for the analytical phase of creatinine clearance determination, Jaffé method is used for creatinine urine determination in most laboratories. It is a sprectrophotometric method with alkaline picrate and continued measurement which has many interference (about 50 non-creatinine substances, such as glucose, ascorbic acid, hydroxybutyrate, acetoacetate)[5]. It has shown that this method gives higher concentrations of creatinine than the enzymatic methods of determination (such as kinetic method which uses enzymes creatininase, creatinase, sarcosine oxidase and phenol-aminophenazone peroxidase). Enzimatic methods are specific than but also more expensive than the economic Jaffé method.

The most sensitive methods for determining GFR are those that use radioisotopes. Literature describes methods with radioactive markers ^{51}Cr-EDTA, ^{99}Th-DTPA and ^{125}I-iotalamat[6]. There is also a non-radioactive iohexol method of direct GFR determination[7]. These methods, as well as those that use inulin clearance, are more costly and more impractical than indirect GFR determination.

Another advantage of eGFR determination is that it eliminates the need for collection of 24-hour urine and use of Jaffé method for urine creatinine determination, as both can be a source of error in measuring creatinine clearance. Cockcroft-Gault equation for estimation of GFR contains data for age, weight and serum creatinine concentration (that is determined by a more specific enzymatic method)[8]. Equation that is a product of Modification of Diet in Renal Disease study (MDRD equation) uses data for serum creatinine concentration and the age of patient[2]. Equation derived from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI equation) in some studies has been found to be the best for estimating GFR in population with higher glomerular filtration rates (>60 ml/min per 1.73 m^2)[9]. It contains serum creatinine concentration and age of patient, but unlike the previous two equations, it is calculated in two ways depending on the creatinine concentration[3]. While some studies show that Cockcroft-Gault equation is the best for estimation of glomerular filtration rate in obese patients[10], others claim that this equation overestimates GFR in obese patients because it relies on total body weight[12]. Obesity has been associated with glomerular hyperfiltration which can be the cause of altered eGFR compared to direct GFR measurement[12]. Similar controversies arose in assessment of creatinine clearance. It has been known to give falsely elevated results in obese patients because it uses body surface area which is disproportionately affected by fat mass, thus these patients have a higher body surface area and lower muscle mass and creatinine production compared to non-obese patients[14]. In diabetic patients falsely elevated results of creatinine clearance have been reported due to the too high creatinine concentrations measured by Jaffé method in ketoacidosis. Pronounced hyperglycemia, osmotic diuresis and reduction in extracellular volume can make creatinine concentrations vary within a large range, especially in the initial stage of diabetes mellitus[5]. Recently, glycated albumin and hemoglobin A1c have been associated with overestimation of eGFR based on serum creatinine. New formulae for eGFR corrected by glycemic control were purposed to be better than the original eGFR, particularly in diabetic patients[14]. Therefore we decided to test all equations in obese and non-obese as well as in diabetic and in non-diabetic patients.

Cystatin C has been shown to be a good endogenous marker of glomerular filtration, because it is synthesized by all body cells at a constant rate (even in the presence of inflammatory conditions), removed from circulation by glomerular filtration and completely reabsorbed and broken down in the tubules, but not secreted by the tubules[15]. Cystatin C has a high intra-individual biological variability similar to creatinine (cystatin C 4.6% and creatinine 6.1%) so it is not that useful for detecting initial changes in glomerular filtration rate, and similar to creatinine, seems to be inadequate for discrimination between healthy individuals and those with decreased kidney function[16]. It is useful for monitoring recovery of patients kidney function after a kidney donation[16], and it has been proven more sensitive than creatinine clearance in two meta-analysis[17,18], but routine use of this marker is still limited by his high cost.

The main goals of this study were to determine how these three equations predict creatinine clearance, which of these equations is the most useful for that, and does old age, obesity, diabetes mellitus or stage of kidney disease affect this prediction. Most guidelines for kidney glomerular filtration use eGFR, but most Croatian hospital laboratories determine creatinine clearance. Is it unbiased to compare their values? Are there any limitations to using them simultaneously? We aimed to determine if there was a significant difference in CrCl and eGFR in all patients, and in any of subgroups (old age, obesity, diabetes mellitus, G-stage of CKD). Also we tested correlations between CrCl and eGFR in all patients and each subgroup.

Materials and Methods

In this retrospective study we compared four ways of assessing glomerular filtration rate, using creatinine clearance, Cockcroft-Gault equation, MDRD equation and CKDI-EPI equation. These parameters were calculated for 500 patients from four internal wards (nephrology, dialysis, endocrinology and hematology) using serum and

TABLE 1
EQUATIONS USED TO CALCULATE GLOMERULAR FILTRATION RATE

Reference	Equation
Thomas[5]	CrCl = uCr (μmol/L) × V (ml) × 1.73 / sCr (μmol/L) × BSA (m^2)
Cockcroft et al.[10]	C-G = [140 – age (years)] × weight (kg) × 1.23 [if male] / sCr (μmol/L)
Levey et al.[2]	MDRD = 32788 × sCr (μmol/L) $^{-1.154}$ × age (years)$^{-0.203}$ × 0.742 [if female] × 1.212 [if black]
Levey et al.[3]	CKD-EPI = 141 × min(sCr / K,1)$^{\alpha}$ × max(sCr / K,1)$^{-1.209}$ × 0.993^{age} × 1.018 [if female] × 1.159 [if black]

CrCl – Creatinine Clearance; uCr – Urine Creatinine; V – volume of 24-hour urine; sCr – Serume Creatinine Concentration; BSA – Body Surface Area; C-G – Cockcroft-Gault; MDRD – Modification of Diet in Renal Disease; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration; K – 0.7 for female and 0.9 for male; α – 0.329 for female and – 0.411 for male

urine analysis done in the last two years. We tried to include patients with a variety of pathophysiological conditions (because those conditions are mostly unknown in our clinical laboratory practice). Exclusion criteria were: inadequate 24-hour urine collection (creatinine coefficient above or over reference interval) and young age (<18 years). We compared creatinine clearance with each of these equations. The equations are listed in Table 1.

We enrolled 235 males (age 18 to 83 years, median 58 years, 95% CI 56–60 years) and 265 females (age 19 to 86 years, median 60 years, 95 % CI 57-62 years). The patients were divided into those younger than 65 years (N=332) and those who were 65 or older (N=168). There was a similar number of diabetics (N=267) and non-diabetics (N=233). According to the body mass index, the patients were divided into a subgroup with BMI<25 (N=141) and those with BMI≥25 (N=359). In all these subgroups we tested for correlation between GFR and CrCl.

To test those equations within different stages of CKD we divided the patients according to the CrCl into G stages, based on KDOQI classification of CKD (with additional subdivision to G3a and G3b stage). G0 was the stage that we introduced to help us distinguish patients with normal creatinine clearance to those with and those without proteinuria (G0 patients had creatinine clearance >89.9 ml/min per 1.73 m^2 and proteinuria ≤150 mg/day, and G1 patients had creatinine clearance >89.9 ml/min per 1.73 m^2 and proteinuria >150 mg/day).

Serum creatinine was analyzed by enzymatic method which used enzymes creatininase, creatinase, sarcosine oxidase and phenol-aminophenazone peroxidase[19], and urine creatinine was determined by Jaffé kinetic method on Bechman Coulter AU680 and AU640 analyzers (Beckman Coulter Inc., Brea, California, SAD). The reference material for enzymatic measurements was Beckman Coulter two level system calibrator, which was traceable to The National Institute of Standards and Technology (NIST) SRM 967 (GC-MS and LC-MS methods were used to certify SRM 967 Creatinine in Human Serum). For urinary measurements of creatinine we used a Beckman Coulter urine calibrator traceable to a reference method based on isotope dilution-mass spectrometry (ID-MS)[20].

Statistical analysis was done by Kolmogorov-Smirnov test and bivariate correlation. Correlation tests were done in SPSS 19 (IBM, Armonk, New York, SAD). Test results were considered significant at $p<0.05$. Passing-Bablok regression, ROC curves and multiple variable graphs were done using MedCalc 12 (MedCalc Software, Ostend, Belgium).

Results

Correlations of CG, MDRD, CKD-EPI and creatinine clearance are presented in the Table 3. The measurements within all groups showed normal distribution and strong correlation of eGFR with CrCl. When tested in the whole group of patients the highest correlation was found between MDRD equation and creatinine clearance (r=0.904), but it was similar to correlation of CKD-EPI equation and CrCl (r=0.897). This was similar regardless of patient age and presence of excess body weight or diabetes mellitus. MDRD and CKD-EPI predict over 77.5% of creatinine clearance variability within all of the groups. Correlation between CG equation and creatinine clearance was lower than are those of newer equations and, within all groups except in patients age 65 or older, CG equation can predict less than 77.5% of creatinine clearance variability.

To discriminate patients with normal and decreased GFR we used a cut off creatinine clearance of 90 ml/min per 1.73 m^2. Area under the curve for Cockcroft-Gault equation was 0.935 (95% CI 0.909 – 0.955) with sensitivity 86.6% and specificity of 87.0%. Optimal cut off for distinguishing normal from pathological creatinine clearance with Cockcroft-Gault equation was 85.03 ml/min per 1.73 m^2. When the same creatinine clearance cut off was used for MDRD equation area under the curve was 0.959 (95% CI 0.938 – 0.975), with diagnostic sensitivity 80.8% and specificity 99.3%. Optimal cut off for in distinguishing normal from pathological creatinine clearance with MDRD equation was 67.91 ml/min per 1.73 m^2. For CKD-EPI equation area under the curve was 0.962 (95% CI 0.941 – 0.977), diagnostic sensitivity 87.90% and specificity 93.80%. The cut off that distinguished normal and pathological creatinine clearance with that equation is 74.36 ml/min per 1.73m^2. There was no statistical difference between AUC of MDRD and CKD-EPI equation (p=0.1116). Figure 1 shows comparison of ROC plots for these three equations.

To discriminate patients with moderately and mildly decreased GFR we used a cut off of 60 ml/min per 1.73 m^2.

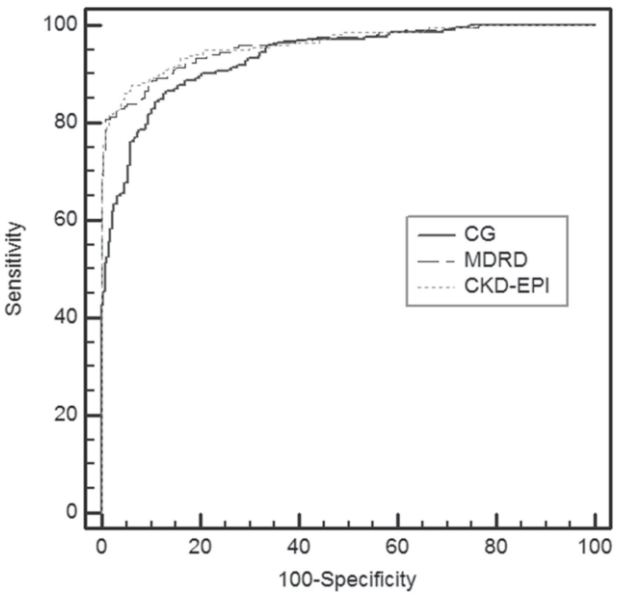

Fig. 1. ROC plots for the diagnostic accuracy of GFR equations in distinguishing between normal and mildly decreased GFR (cut off at CrCl 90 ml/min per 1.73 m²). CrCl – creatinine clearance; C-G – Cockcroft-Gault; MDRD – modification of diet in renal disease; CKD-EPI – Chronic kidney disease epidemiology collaboration.

Area under the curve for Cockcroft-Gault equation was 0.969 (95% CI 0.949 – 0.982), with sensitivity 88.7% and specificity 91.7%. Cut off for Cockcroft-Gault estimated GFR to distinguish the division was determined at 64.68 ml/min per 1.73 m². When the creatinine clearance of 60 ml/min per 1.73 m² was used as a criterion for MDRD equation, the AUC was 0.983 (95% CI 0.967 – 0.992) with sensitivity of 90.8% and specificity of 94.5%. Cut off for GFR estimated by MDRD was set at 56.04 ml/min per 1.73 m². For CKD-EPI equation AUC was 0.982 (95% CI 0.966 – 0.992) at diagnostic sensitivity of 93.4% and specificity of 90.8% for discriminating mild and moderately decreased GFR in our study group. The cut off was estimated at GFR of 54.41 ml/min per 1.73 m² using CKD-EPI equation. There was no statistical difference found between AUC for MDRD and CKD-EPI (p=0.5023). Figure 2 shows ROC plots for this analysis.

The number of patients with normal CrCl (>90 ml/min per 1.73 m²) and decreased eGFR was highest in the group of overweight patients (BMI≥25). MDRD and CKD-EPI showed higher number of patients with normal CrCl and decreased eGFR, and the ratio of overweight patients within those „normal CrCl and decreased eGFR" group for these two methods was over 91% (Table 4).

When observing only obese subjects (N=359), 9.75% of them had normal CrCl (>89 ml/min/1.73m²) and de-

TABLE 2
DIVISION OF PATIENTS BASED ON G-STAGES OF CHRONIC KIDNEY DISEASE (EACH G-STAGE IS DEFINED BY CREATININE CLEARANCE RANGE)

G-stage	G0*	G1*	G2	G3a	G3b	G4	G5
Creatinine clearance (ml/min per 1.73 m²)	>89.9	>89.9	60-89.9	45-59.9	30-44.9	15-29.9	<15
N (patients)	147	129	115	40	26	26	17

*G0 and G1 patients have normal creatinine clearance but patients in G1 have proteinuria. G-stage – category of chronic kidney disease based on glomerular filtration rate.

TABLE 3
PEARSON'S r AND r2 FOR CREATININE CLEARANACE vs. ESTIMATED GLOMERULAR FILTRATION RATE EQUATIONS IN OUR PATIENT GROUPS

	CrCl *vs.* CG equation		CrCl *vs.* MDRD equation		CrCl *vs.* CKD-EPI equation	
	Pearson's r	r²	Pearson's r	r²	Pearson's r	r²
All patients (N=500)	0.860	0.740	0.904	0.817	0.897	0.802
Age <65 years (N=332)	0.851	0.724	0.888	0.788	0.881	0.776
Age ≥65 years (N=168)	0.905	0.819	0.920	0.846	0.919	0.845
BMI <25 (N=141)	0.878	0.771	0.921	0.848	0.912	0.832
BMI ≥25 (N=359)	0.863	0.745	0.914	0.835	0.912	0.832
Non-diabetic (N=233)	0.869	0.755	0.914	0.835	0.908	0.824
Diabetic (N=267)	0.853	0.728	0.894	0.799	0.886	0.785

CrCl – Creatinine Clearance; C-G – Cockcroft-Gault; MDRD – Modification of Diet in Renal Disease; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration; BMI – Body Mass Index. p<0.001

TABLE 4

NUMBER OF NORMAL CrCl (>89 ml/min per 1.73 m^2) AND DECRESED eGFR (<90 ml/min per 1.73 m^2)

	Number (percentage) of »normal CrCl and decresed eGFR« in all patients	Number (percentage) of overweight patients in »normal CrCl and decresed eGFR« group
Cockcroft-Gault	54 (10.8%)	35 (64.81%)
MDRD	88 (17.6%)	81 (92.04%)
CKD-EPI	81 (16.2%)	74 (91.36%)

CrCl – creatinine clearance; C-G – Cockcroft-Gault; MDRD – modification of diet in renal disease; CKD-EPI – Chronic kidney disease epidemiology collaboration

TABLE 5

PEARSON'S r AND r^2 FOR CREATININE CLEARANCE *vs*. ESTIMATED GLOMERULAR FILTRATION RATE EQUATION IN OUR PATIENTS CONSIDERING THE STAGES OF CHRONIC KIDNEY DISEASE

	CrCl *vs*. CG equation		CrCl *vs*. MDRD equation		CrCl *vs*. CKD-EPI equation	
	Pearson's r	r^2	Pearson's r	r^2	Pearson's r	r^2
G0 stage of CKD (N=147)	0.564*	0.318*	0.623*	0.388*	0.619*	0.383*
G1 stage of CKD (N=129)	0.628*	0.394*	0.714*	0.510*	0.708*	0.501*
G2 stage of CKD (N=115)	0.350*	0.122*	0.435*	0.189*	0.420*	0.176*
G3a stage of CKD (N=40)	0.241†	0.058*	0.316‡	0.100*	0.266§	0.071*
G3b stage of CKD (N=26)	0.452‡	0.204*	0.472‡	0.223*	0.487‡	0.237*
G4 stage of CKD (N=26)	0.751*	0.564*	0.617*	0.380*	0.602*	0.363*
G5 stage of CKD (N=17)	0.087‖	0.008*	0.425¶	0.181*	0.383**	0.147*

*p<0.001, †p=0.13, ‡p<0.05, §p=0.097, ‖p=0.739, ¶p=0.089, **p=0.129. CrCl – creatinine clearance; C-G – Cockcroft-Gault; MDRD – modification of diet in renal disease; CKD-EPI – Chronic kidney disease epidemiology collaboration; G-stage – category of chronic kidney disease based on glomerular filtration rate; CKD – chronic kidney disease

creased Cockcroft-Gault GFR (<90 ml/min/1.73m^2), 22.56% of them had normal CrCl and decreased MDRD GFR, and 20.61% had normal CrCl and decreased CKD-EPI.

Table 5 shows the patients' distribution based on the G stage of CKD and correlations of Cockcroft-Gault, MDRD, CKD-EPI and creatinine clearance within each G stage. Measurements in all subgroups showed normal distribution and moderate to good correlation between eGFR and CrCl, with exceptions in G3a and G5 stage for Cockroft-Gault (no significant correlation) and G4 stage for Cockcroft-Gault (very good correlation with creatinine clearance).

In patients with moderate to severe decreased GFR Cockcroft-Gault equation showed the lowest precision in assessment of GFR (figure 3). GFR estimated by Cockcroft-Gault showed the most dispersion of eGFR values compared with other eGFR.

Using Passing and Bablok regression patients in G stage were tested to see if there was a difference between CrCl and each GFR equation. There was a systematic, proportional or both differences found between CrCl and eGFR in all G stages except when comparing CrCl with MDRD and CrCl with CKD-EPI in G4 and G5 stage (figure 4 and figure 5).

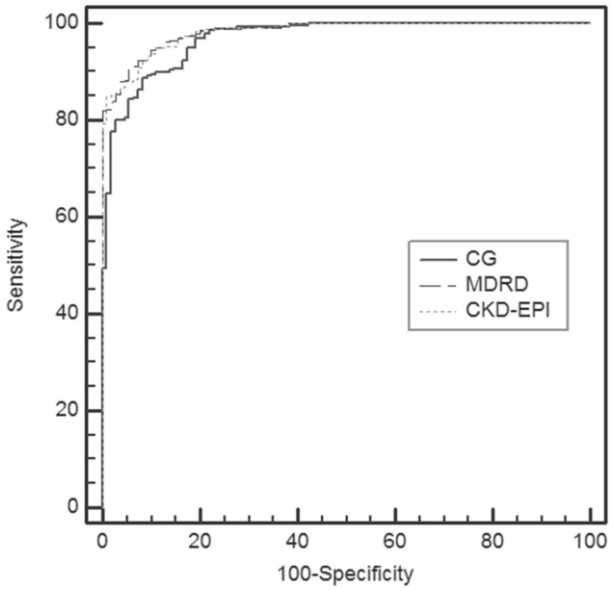

Fig. 2. ROC plots for the diagnostic accuracy of GFR equations in distinguishing between mildly and moderately decreased GFR (cut off at CrCl 60 ml/min per 1.73 m^2). CrCl – creatinine clearance; C-G – Cockcroft-Gault; MDRD – modification of diet in renal disease; CKD-EPI – Chronic kidney disease epidemiology collaboration.

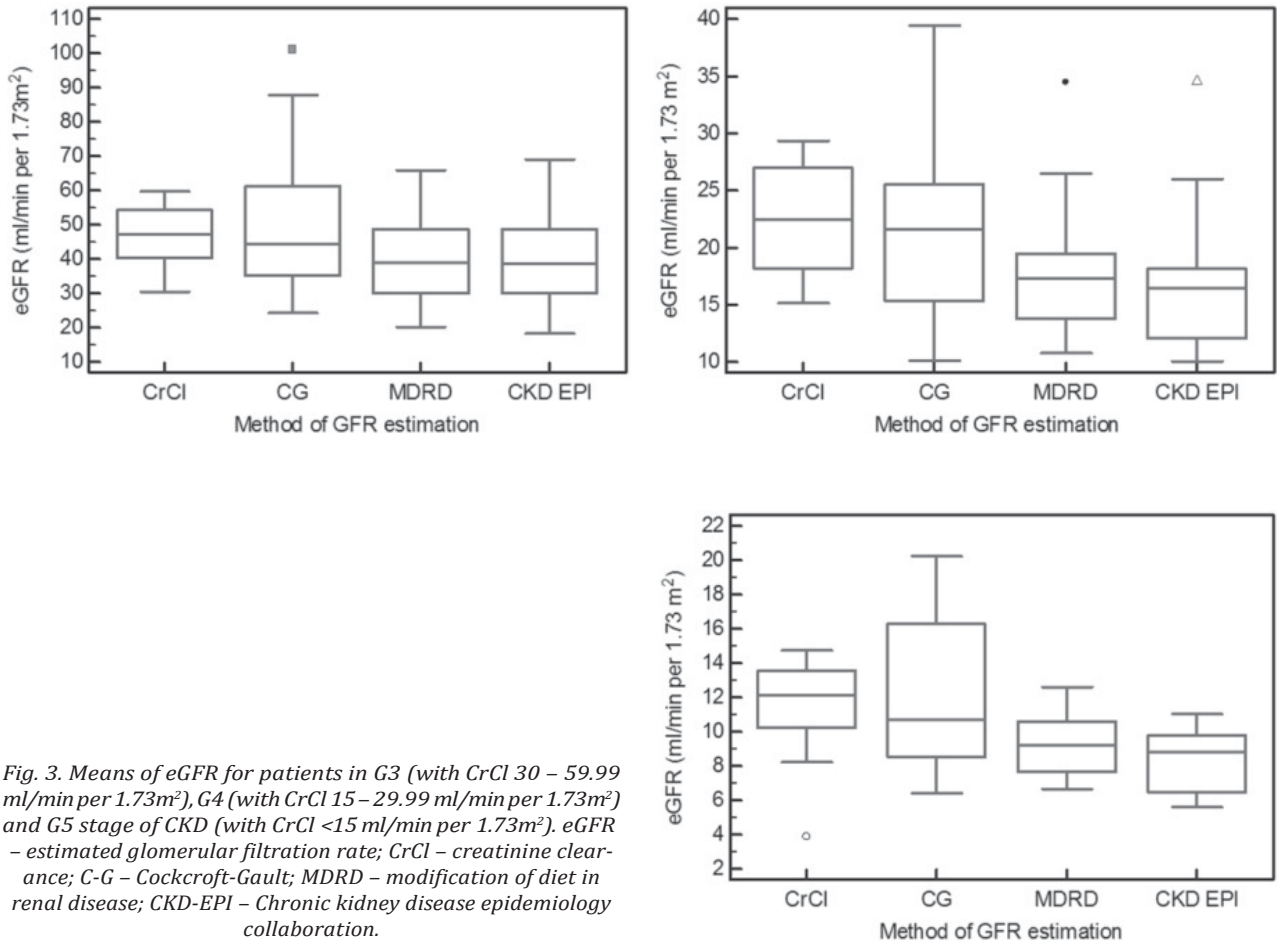

Fig. 3. Means of eGFR for patients in G3 (with CrCl 30 – 59.99 ml/min per 1.73m²), G4 (with CrCl 15 – 29.99 ml/min per 1.73m²) and G5 stage of CKD (with CrCl <15 ml/min per 1.73m²). eGFR – estimated glomerular filtration rate; CrCl – creatinine clearance; C-G – Cockcroft-Gault; MDRD – modification of diet in renal disease; CKD-EPI – Chronic kidney disease epidemiology collaboration.

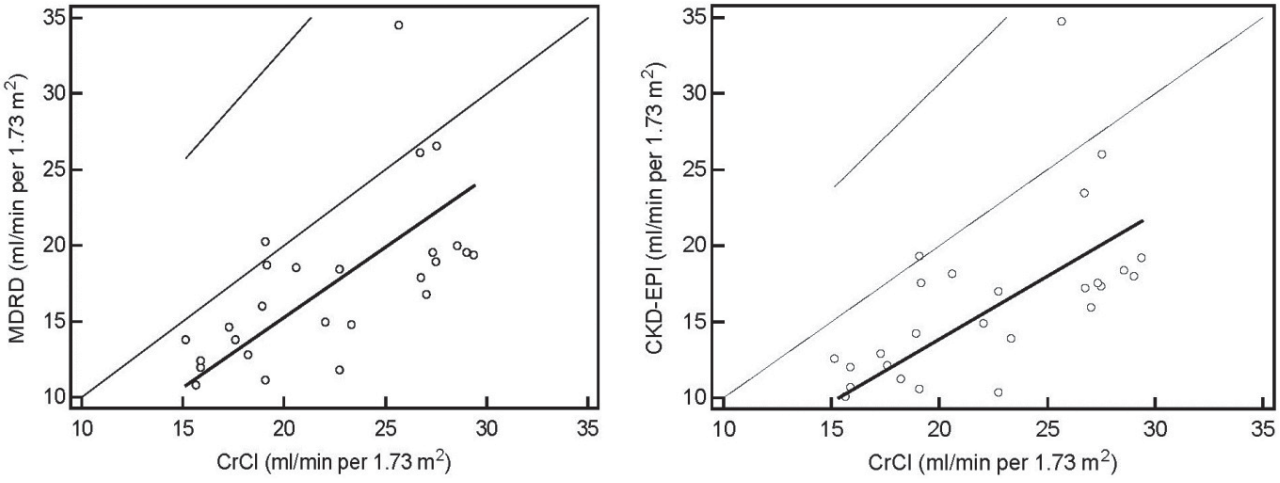

Fig. 4. Passing-Bablok regression for MDRD and CKD-EPI for patients in G4 stage of CKD (with CrCl 15 – 29.99 ml/min per 1.73m²). Regression equation for MDRD is y = –3.209929 + 0.924171 x (with 95% CI for intercept from –14.6113 to 3.1105 and 95% CI for slope from 0.5875 to 1.4958). Regression equation for CKD-EPI is y = –2.659065 + 0.825766 x (with 95% CI for intercept from –14.0703 to 2.7325 and 95% CI for slope 0.5489 to 1.3966). CrCl – creatinine clearance; MDRD – modification of diet in renal disease; CKD-EPI – Chronic kidney disease epidemiology collaboration.

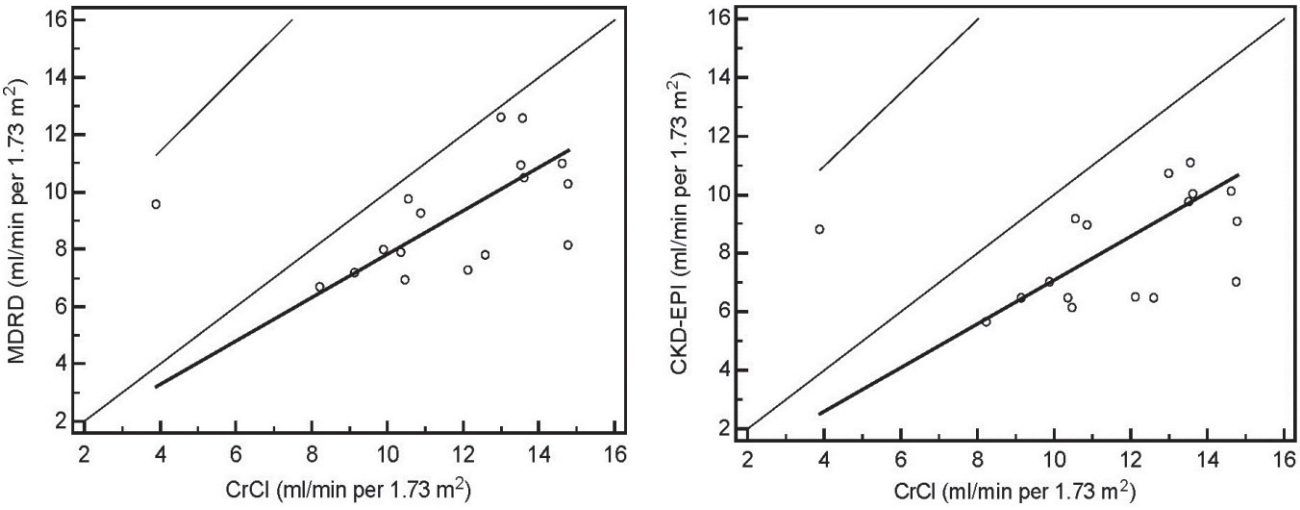

Fig. 5. Passing-Bablok regression for MDRD and CKD-EPI for patients in G5 stage of CKD (with CrCl <15 ml/min per 1.73m^2). Regression equation for MDRD is y = 0.244239 + 0.758007 x (with 95% CI for intercept from –5.7020 to 6.1797 and 95% CI for slope from 0.2767 to 1.3120). Regression equation for CKD-EPI is y = –0.415452 + 0.750046 x (with 95% CI for intercept from –6.5093 to 5.9613 and 95% CI for slope 0.2110 to 1.2528). CrCl – creatinine clearance; MDRD – modification of diet in renal disease; CKD-EPI – Chronic kidney disease epidemiology collaboration.

Discussion

Statistical analysis of ROC plots for diagnostic accuracy of MDRD and CKD-EPI in predicting CrCl did not show statistical difference in their performance. However they both had significantly better diagnostic concordance than C-G equation. This concordance was greater at cut off 90 ml/min per 1.73 m^2, as well as at cut off 60 ml/min per 1.73 m^2.

In the group of patients younger than 65 years, as well as in older patients, MDRD equation showed the highest correlation with CrCl, respectively. Interestingly, the ability to predict CrCl was higher in older patients, regardless witch equation we used. ROC plots at cut off CrCl 60 ml/min per 1.73 m^2 for older patients showed almost identical AUC (0.978 for C-G and MDRD, and 0.977 for CKD-EPI) and there was no statistical difference found between them (data not shown). This could mean that changes in GFR at older age are not physiological as it was previously presumed, but rather a sign of kidney disease. In the group of diabetics, as well as non-diabetics, MDRD equation showed the highest correlation with CrCl, respectively. All equations have been better in predicting CrCl in non-diabetics than in diabetics. A possible reason is hyperfiltration of the glomeruli in the initial stage of diabetes mellitus that affects CrCl (increasing urinary excreted creatinine and urine volume) but not the eGFR. Another possible reason for discrepancies in eGFR and CrCl is that eGFR formulas rely only on one measurement, serum creatinine by enzymatic method, while CrCl calculation also includes urinary creatinine measurement by Jaffé method. Each of these methods has their own interferences. Enzymatic creatinine assay has less interferences but is not completely specific to creatinine (interferences of dopamine and dobutamine have been reported). Acetoacetate, glucose and hydroxybutirate have been reported as interference in the Jaffé method. [20] They can be found in urine of diabetic patients in cases of ketonuria. These interferences could, in theory, be responsible for overestimation of GFR by CrCl in diabetic patients, or be a source for variability in CrCl when compared with eGFR. ROC plots at cut off CrCl 60 ml/min per 1.73 m^2 for diabetic patients showed almost identical AUC for MDRD (0.989) and for CKD-EPI (0.987). Also, there was no statistical difference found between them (data not shown). In the group of obese, as well as in non-obese patients, MDRD showed similar correlations with CrCl (0.914 for obese and 0.921 for non-obese patients), and CKD-EPI had an identical Pearson's correlation coefficient with CrCl in obese and non-obese patients (0.912). C-G equation didn't have as strong correlation as the other two equations but it had a lowest number of subjects with normal CrCl and decreased eGFR when compared with higher percentage of those subjects obtained when using MDRD and CKD-EPI (table 4). Furthermore, the ratio of obese subjects in »normal CrCl and decresed eGFR« group was 27% higher in MDRD and CKD-EPI calculations than when using C-G equation. This could mean that the use of BSA (body surface area) in CrCl did not artificially lowered GFR and mask any ongoing glomerular hyperfiltation in obese subjects (due to the effect of fat mass on BSA) as some authors previously suggested[14]. It is not likely that the CrCl in obese patients was higher than eGFR due to Jaffé method for urine creatinine determination, because subjects with normal CrCl and decreased eGFR would then be registered in the other subject groups as well, and not mostly in the obese group. There is a possibility that the eGFR were better at determining GFR in

obese patients, and that CrCl overestimated GFR. The fact that percentage of obese patients in »normal CrCl and decreased eGFR« is almost identical in case of MDRD and CKD-EPI, and these two equations don't rely on BSA or weight, could also be an indicator of a more accurate GFR estimation by these equations that by CrCl. These obese patients should be further investigated by the use of cystatin C or some other method that is not as dependent to muscle mass as serum creatinine.

When patients were grouped by G stage, the distribution of eGFR within each group was normal. Estimated GFR showed various degree of correlation with CrCl, with various significance (see table 5). The highest correlation was found between MDRD and creatinine clearance in all groups tested except in case of patients in G3b stage where CKD-EPI showed the highest correlation with CrCl, and G4 stage of CKD, where GFR estimated by Cockcroft-Gault showed the highest correlation with CrCl. In all other groups GFR estimated by Cockcroft-Gault had the lowest correlation with CrCl, and even no correlation in G3a and G5 stages. When compared with very good correlation measured between larger groups (140 patients or more) in table 3, the correlation seen in G stage groups with 40 patients or less is mostly only moderate. Due to the small number of patients in stages G3 to G5 we cannot be sure whether this was caused by different performance of eGFR formulas in patient with moderate to decreased kidney function or just an effect of a smaller number of patients in those groups. In future research it would be useful to get a larger group of patients with more advanced stages of CKD.

In patients with moderate to severe decreased GFR Cockcroft-Gault equation showed lower precision in assessment of GFR than CrCl, and Passing-Bablok regression showed no agreement between CrCl and Cockcroft-Gault equation that in any of the G stages. In cases of MDRD and CKD-EPI, Passing and Bablok regression showed that only in stages of severely decreased GFR (G4 and G5) we could use CrCl and MDRD, or CrCl and CKD-EPI, simultaneously and interchangeably, respectively. In less severe stages of GFR to exchange CrCl with one of the equations would be bias, because they have either a systematic or proportional difference between them, or both. This should be confirmed in studies with larger patient groups in the advanced stages of CKD.

The limitations of this study were the fact that it is retrospective and that it lacked a gold standard measurement of GFR. The CKD-EPI equation in some studies has been found to be the best for estimating GFR in population with higher glomerular filtration rates (>60 ml/min per 1.73 m^2)[11]. Our study has not shown that it is better than MDRD in doing so, at least at CrCl values >60 ml/min per 1.73 m^2. In our study CrCl has been shown to overestimate GFR in overweight patients. As a marker of weight we used BMI, which does not separate muscular mass and adipose tissue, so it is not adequate in patients with increased muscular mass. Since CrCl is dependent on muscle mass further studies should use a marker that is not dependent on body constitution, such as cistatin C or radioactive markers, for the determination if CrCl is overestimating GFR in obese patients. To minimize the secretion of creatinine by renal tubule, Lezaić et al. used a drug cimetidine that blocks tubular secretion of creatinine[7]. This seems to be a good way to limit the variations in urinary creatinine excretion when using CrCl as a marker of GFR or in the absence of exact measurement of renal clearance (iohexol clearance, inulin clearance or radioactive marker).

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Abbreviations:

C-G – Cockcroft-Gault equation
MDRD – Modification of Diet in Renal Disease Study equation
CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration equation
BMI – Body-Mass Index
CrCl – Creatinine Clearance
KDIQO – Kidney Disease Outcomes Quality Initiative
CKD – Chronic Kidney Disease
eGFR – Estimated Glomerular Filtration Rate
BSA – Body Surface Area
uCr – Urine Creatinine
sCr – Serume Creatinine
NIST SRM 967 – The National Institute of Standards and Technology Standard Reference Material
ID-MS – Isotope Dilution-Mass Spectrometry
ROC – Receiver Operating Characteristic
AUC – Area Under the Curve

KLIRENS KREATININA I FORMULE ZA RAČUNANJE eGFR – MOGU LI SE KORISTITI NAIZMJENIČNO?

S A Ž E T A K

Cilj studije bio je ispitati koja od formula za izračun stope glomerularne filtracije (eGFR, engl. estimated glomerulal filtration rate) je najkorisnija za predviđanje klirensa kreatinina. Koristeći retrospektivni pregled podataka za 500 bolničkih pacijenata izračunali smo stopu glomerularne filtracije prema formulama Cockcroft-Gault (C-G), Modification of Diet in Renal Disease Study equation (MDRD) i Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI). Ispitali smo koliko su rezultati ovih triju formula usporedivi s klirensom kreatinina, te da li stadij bubrežne bolesti, indeks tjelesne mase (BMI, engl. body-mass index), dijabetes ili starija dob utječu na njihovu sposobnost predviđanja klirensa kreatinina. Sve ove formule su pokazale visoku korelaciju s klirensom kreatinina, neovisno o dijabetesu, prekomjernoj tjelesnoj težini ili starijoj dobi. Nije postojala statistička razlika ($p<0,05$) između dijagnostičke točnosti pri usporedbi ROC krivulja za MDRD i CKD-EPI kod graničnih vrijednosti klirensa kreatinina od 60 ml/min/1,73 m^2 i 90 ml/min/1,73 m^2 prilikom analize podataka za sve subjekte, starije subjekte (<65 godina) i dijabetičare. Postotak subjekata s povećanom tjelesnom težinom (BMI>25) u skupini lažno pozitivnih subjekata (onih s normalnim klirensom kreatinina i sniženim eGFR) bio je 64,8% za C-G, 88,6% za MDRD i 88,9% za CKD-EPI. Velik broj subjekata s povećanom tjelesnom težinom i normalnim klirensom kreatinina imao je snižen eGFR, što upućuje na to da klirens kreatinina precjenjuje GFR u subjekata s povećanom tjelesnom težinom. Passing-Bablok regresija je pokazala slaganje između klirensa kreatinina i MDRD, te klirensa kreatinina i CKD-EPI samo u slučajevima ozbiljnije sniženog GFR (G4 i G5 stadij kronične bubrežne bolesti). Samo u ovim stadijima kronične bubrežne bolesti klirens kreatinina i MDRD, te klirens kreatinina i CKD-EPI, se mogu koristiti simultano.