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Equations estimating renal function in patients with diabetes

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KEYWORDS

Chronic kidney disease, CKD-EPI, diabetes, glomerular filtration rate, MDRD

INTRODUCTION

Renal function testing is routinely performed in various patient populations with a wide range of renal function. Impaired renal function is an independent risk factor for (premature) cardiovascular disease.[1] Several traditional (diabetes mellitus (DM) and hypertension) and non-traditional (including endothelial dysfunction and oxidative stress) risk factors seem to play an attributable role, but exact mechanisms and interactions remain to be elucidated.[1] Currently, the glomerular filtration rate (GFR) is considered to be the best overall indicator of renal function.[2]

Gold standards for assessing GFR, such as renal inulin clearance or isotopic methods,[3,4] are cumbersome and costly and therefore reserved for research settings. A less costly and less complex method to measure renal function is the 24-hour creatinine clearance (CrCl). This is the most frequently applied method to assess renal function in daily practice, although collecting 24-hour urine samples is time consuming, and the reliability of the outcome is highly dependent on the accuracy of the urine collection.[5]

Several prediction formulas for estimating renal function have been developed. The four-variable Modification of Diet in Renal Disease equation (MDRD) is the prediction formula that is most frequently used.[2,6] Its advantages and disadvantages have been extensively debated.[7,8] Its major disadvantages include its imprecision and systematic underestimation of GFR in patients with normal to high normal serum creatinine levels, and the underestimation in women and young people.[7,9] To overcome the aforementioned disadvantages, a new prediction equation, the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI), was developed.[10] This formula was developed in a population with predominantly young and middle-aged people (87% ≤65 years) with an average GFR of 68 ml/min/1.73m^2; 43% were female.[10] Potential complementary covariates such as renal transplant, diabetes and weight were considered, but the final equation used the same variables as the MDRD equation.[11] Therefore, it is not clear whether the CKD-EPI can be applied in all populations. Since an accurate estimate of renal function is important and renal function is frequently assessed in diabetic patients, we wanted to evaluate the performance of the CKD-EPI and the MDRD equations in a large, anthropometrically diverse cohort of diabetic patients.

MATERIALS AND METHODS

This retrospective observational cross-sectional study was conducted at the diabetes outpatient clinic of the Maxima Medical Centre in Eindhoven, the Netherlands. A total of 1097 serum creatinine concentration results from adults, previously diagnosed with type 1 or type 2 DM, were collected. An anonymous database was created, using data from the 'Chipsoft Electronisch Zorg Informatie Systeem' [Chipsoft Electronic Care Information System] (CS-EZIS), the computerised medical record system used at the

Maxima Medical Centre. Data collected included 24-hour urinary creatinine (mmol/l), serum creatinine (μmol/l), HbA1c (mmol/mol), weight (kg), height (centimetres), age (years), and gender, all data being collected on the same day, except for the 24-hour urine collection, which was collected in the 24 hours prior to the other measurements. The body mass index (BMI) of each patient was calculated (BMI = weight (kilograms) / height (meters)^2) and added to the database. Ultimately, 916 patients remained eligible for inclusion. Two subjects younger than 18 years and three subjects with an CrCl >250 ml/min were excluded, since the MDRD has not been validated in these patient groups. In 176 cases, subjects had collected two 24-hour urine samples during the indicated period. In these cases, the mean of the two 24-hour CrCls was used.

Medication details and information on comorbidities were not available. Since no information on race was available, all patients were considered to be Caucasian. No formal approval from the Medical Ethics Committee was required, as our data included only anonymous patient characteristics and laboratory data.

Renal function measurements and definitions

The serum creatinine concentration was measured by an enzymatic technique (Modular PA, Roche), and validated by isotope dilution mass spectrometry (IDMS). Renal function was estimated by two different eGFR equations, the MDRD and the CKD-EPI (*table 1*). Twenty-four hour CrCl corrected for body surface area (BSA) was calculated (*table 1*). The Dubois formula was used to calculate the BSA.[12]

Table 1. *Renal function prediction equations*

Equation	Gender	Serum-creatinine (μmol/l)	eGFR (ml/min/1.73m^2)
CKD-EPI	Female	≤62	144 x (IDMS creatinine/ 88.4/0.7)$^{-0.329}$ x (0.993)^{age}
	Female	>62	144 x (IDMS creatinine/ 88.4/0.7)$^{-1.209}$ x (0.993)^{age}
	Male	≤80	141 x (IDMS creatinine/ 88.4/0.9)$^{-0.411}$ x (0.993)^{age}
	Male	>80	141 x (IDMS creatinine/ 88.4/0.9)$^{-1.209}$ x (0.993)^{age}
MDRD	Female	All	175 x (IDMS creatinine/ 88.4)$^{-1.154}$ x age$^{-0.203}$ x 0.742
	Male	All	175 x (IDMS creatinine/ 88.4)$^{-1.154}$ x age$^{-0.203}$
Creatinine clearance	All	All	(urine creatinine [mmol/L] x 1000/serum creatinine [μmol/L]) x (24-hour volume
BSA corrected			urine [ml]/1440) x (1.73 m^2/ BSA)

CKD-EPI = chronic kidney disease epidemiology equation; MDRD = modification of diet in renal disease formula; BSA = body surface area; IDMS = isotope dilution mass spectrometry.

Statistical analysis

Analyses were performed using SPSS 16.0 (SPSS, Chicago, IL). Q-Q plots and histograms were used to assess normality. Continuous variables are represented as mean (± standard deviation) for the normally distributed values and as a median (interquartile range) for the non-normally distributed variables.

Spearman's coefficient of correlation was calculated to determine the correlation between the CrCl and the eGFR calculated by the MDRD and the CKD-EPI formulas. Bland-Altman plots were created showing the mean of two measurement methods (i.e. CrCl and the MDRD / CKD-EPI) against the absolute difference between these two methods. Krippendorff's coefficient, an aggregate measure for method concordance, was calculated (see textbox; 1 meaning perfect concordance and -1 meaning perfect discordance between the two methods), since neither maximum correlation nor agreement in accuracy and precision alone will suffice to prove concordance and thus sufficient reproducibility among methods; this requires $\mu_1=\mu_2$, $\sigma_1^2=\sigma_2^2$ and $\rho=+1$ (μ_1 being the population mean of the CrCl, μ_2 being the population mean of the MDRD or the CKD-EPI, σ_1 and σ_2 being the standard deviation of μ_1 and μ_2 respectively, ρ being the Pearson's correlation coefficient between the CrCl and the MDRD or the CKD-EPI. Krippendorff's coefficient corresponds to the Bland-Altman plot in a similar way as ρ corresponds to the simple scattergram,[13] see textbox.

The bias and precision (see textbox) of both formulas were determined.

Ultimately we evaluated the classification of patients according to the CKD-EPI or the MDRD equation compared with when CrCl is used to classify patients. Moreover, the prevalence of stage III-V CKD in this diabetic population was evaluated per age group.

Bias: Mean difference between the GFR estimating formula and the creatinine clearance corrected for BSA

Precision: Standard deviation of the bias

Krippendorff's coefficient: $K= (2 \times \sigma1 \times \sigma2 \times \rho) / (2 \times \sigma1 \times \sigma2 + (\sigma1 - \sigma2)^2 + (\mu1 - \mu2))^2$

RESULTS

The patient characteristics are presented in *table 2*. Age ranged from 18 to 92 years with 53.6% of the population aged under 65 years. The population represented a wide range of renal function (CrCl 11 to 250 ml/min/1.73m^2). Of the subjects, 71% had a CrCl >60 ml/min/1.73m^2.

Table 2. *Demographic and clinical characteristics*

Characteristic	All
n (%)	916
Sex, male (%)	55.3
Age (year)	63 [53, 72]
HbA1c (mmol/mol)	50 [42, 60]
BMI (kg/m²)	28 [25, 32]
Creatinine (µmol/l)	79 [67, 97]
Creatinine clearance (ml/min/1.73m²)	96 [70, 123]
MDRD (ml/min/1.73m²)	77 ± 25
CKD-EPI (ml/min/1.73m²)	79 ± 24

Data are presented as number (%) or median [interquartile range].

Table 3. *Precision of eGFR prediction equations*

Creatinine clearance		MDRD		CKD-EPI	
(ml/min/1.73m²)	n	Bias	Precision	Bias	Precision
>90	521	-53.4	35.2	-51.4	34.8
60-90	248	-19.0	18.6	-16.4	18.6
45-59.9	85	-9.4	15.2	-8.5	16.5
30-44.9	44	0.9	20.4	1.2	20.0
<30	18	8.4	21.3	8.7	24.0
All	916	-36.2	35.7	-34.2	35.3

Precision (ml/min/1.73m²), defined as the standard deviation of the mean difference between the estimated glomerular filtration rate (estimated by the modification of diet in renal disease formula (MDRD) and the chronic kidney disease epidemiology collaboration equation (CKD-EPI)) and the creatinine clearance, is shown per creatinine clearance stage. CI=confidence interval.

The correlation and Krippendorff's coefficient

The correlation was 0.75 and 0.76 between the MDRD and the CKD-EPI, respectively, and the Crcl. *Figure 1* shows the Bland-Altman plots that evaluate the extent of agreement between the CrCl and both GFR estimating equations. Krippendorff's coefficient, demonstrating the method concordance between both GFR prediction equations and the CrCl, was almost equally large for the MDRD and the CKD-EPI: 0.54 and 0.57, respectively.

Bias and precision

The results for the bias and the precision are presented in *table 3*. The bias of the MDRD and the CKD-EPI compared with the Crcl was -22 (±26) and -20 (±26) ml/min/1.73m², respectively (p<0.01 for both). Both the MDRD and the CKD-EPI showed a large bias and imprecision in all CrCl categories, which was most prominent in people with a CrCl >90 ml/min/1.73m²: -53.4 (±35.2) and -51.4 (±34.8) ml/min/1.73m² for the MDRD and the CKD-EPI, respectively.

eGFR prediction formulas and staging

Figures 2A and *2B* represent the eGFR values for both formulas by age and gender. For both the CKD-EPI and the MDRD a steep decline in eGFR was observed with ageing. When compared with the MDRD-4, the CKD-EPI gave higher estimates of GFR at young age (≤65 years). At older age, MDRD-4 and CKD-EPI gave a similar estimation of GFR. The influence on CKD staging using the CKD-EPI or MDRD formula is illustrated in *tables 4A* and *4B*, for

Figure 1. *Bland-Altman plots comparing the creatinine clearance and the estimated glomerular filtration rate, calculated by the Modification of Diet in Renal Disease formula or the Chronic Kidney Disease Epidemiology Collaboration equations. The upper and lower horizontal lines represent the upper (+2 SD) and lower (-2 SD) limits of agreement. The horizontal line in the middle represents the mean difference between the creatinine clearance and the GFR estimating equations*

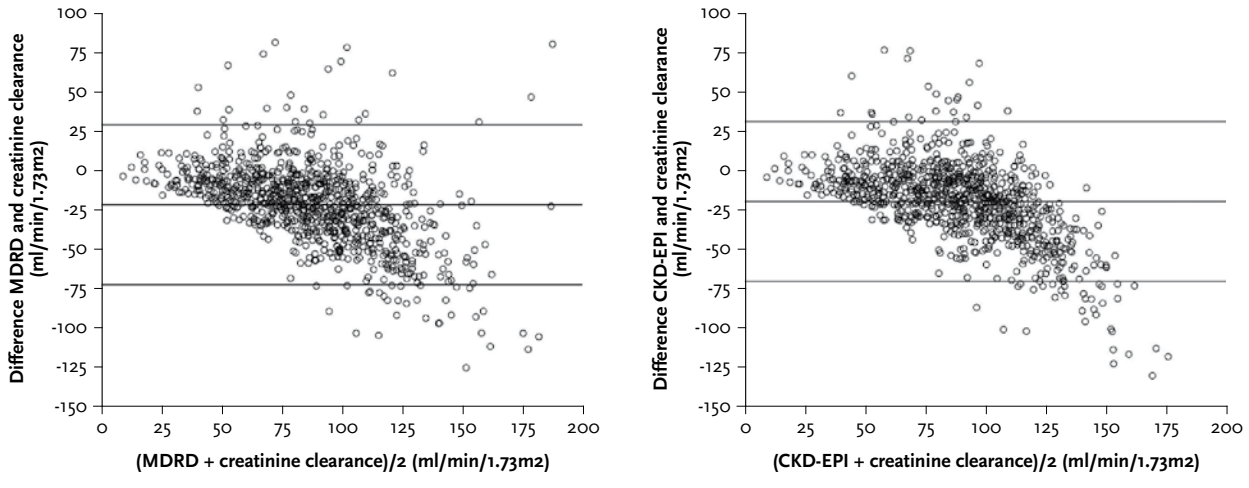


Figure 2a. *Men: The dashed lines represent the 5th percentile, the median and the 95th percentile of the CKD-EPI. The black line represents the 5th percentile, the median and the 95th percentile of the MDRD*

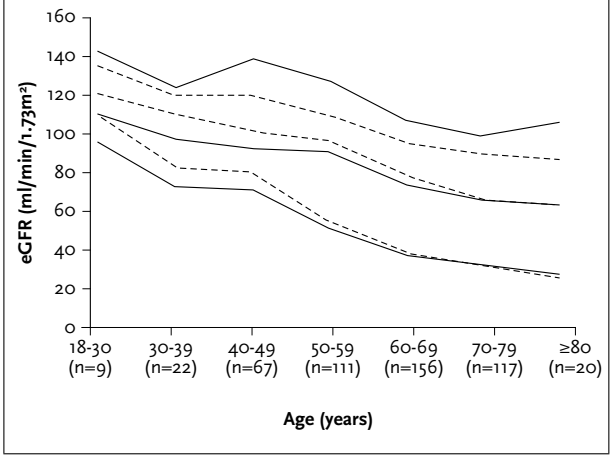
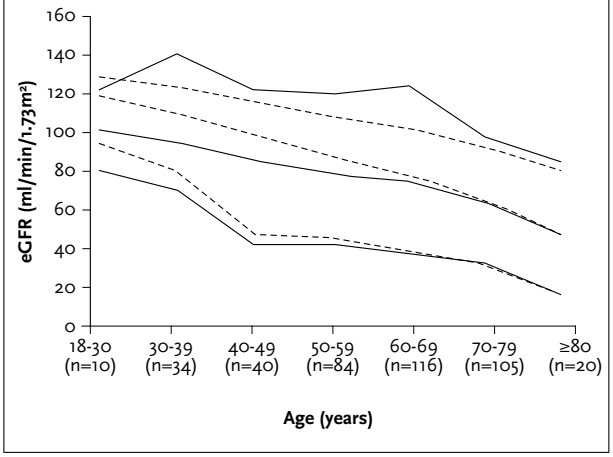


Figure 2b. *Women: The dashed lines represent the 5th percentile, the median and the 95th percentile of the CKD-EPI. The black line represents the 5th percentile, the median and the 95th percentile of the MDRD*



men and women respectively. Smaller stages than those given in the KDOQI guidelines are used to provide more detailed insight. These tables clearly demonstrate that the CKD-EPI provides higher eGFR values than the MDRD, specifically at higher levels of eGFR and in women (along the total range of renal function). Of the women 26.4% were categorised in a lower CKD stage using the CKD-EPI. *Figure 3* presents the consequence of the introduction of the CKD-EPI on the prevalence of stage III-V CKD. A decline in the number of young people (<65 years) diagnosed with stage III-V is observed, from 12.6 to 10.7%. In the elderly patient category, the numbers of diagnosed patients remains similar using the CKD-EPI or the MDRD.

Table 4A. *Estimated GFR stage for males using the CKD-EPI or MDRD formula*

	CKD-EPI (ml/min/1.73m²)						
MDRD (ml/min/1.73m²)							
	<30	30-44	45-59	60-74	75-89	>90	Total
<30	**10**						10
30-44	1	**34**					35
45-59		2	**56**	6			64
60-74				**81**	27		108
75-89					**74**	40	114
>90					13	**163**	176
Total	11	36	56	87	114	203	**507**

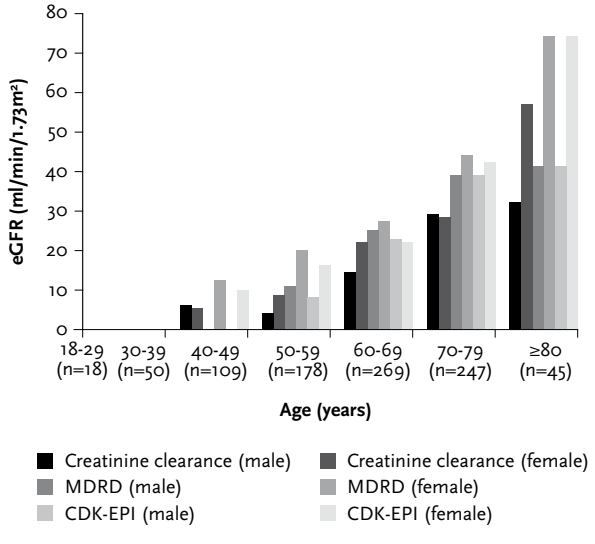
Numbers represent absolute numbers. Blank cells have no observations. CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration Equation; MDRD = Modification of Diet in Renal Disease formula (MDRD).

Table 4B. *Estimated GFR stage for females using the CKD-EPI or MDRD formula*

	CKD-EPI (ml/min/1.73m²)						
MDRD (ml/min/1.73m²)							
	<30	30-44	45-59	60-74	75-89	>90	Total
<30	**12**	2					14
30-44		**30**	11				41
45-59		1	**51**	12			64
60-74				**60**	38		98
75-89					**50**	45	95
>90					5	**92**	97
Total	12	33	62	72	93	137	**409**

Numbers represent absolute numbers. Blank cells have no observations. CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration Equation; MDRD = Modification of Diet in Renal Disease formula (MDRD).

Figure 3. *Prevalence of Chronic Kidney Disease (CKD) stage III-V (eGFR < 60 ml/min/1.73m²) in Dutch diabetic male and female patients*



DISCUSSION

In this study, we evaluated the performance of the CKD-EPI as a new method of estimating renal function in diabetic patients with a wide range of renal function. When using CrCl as the comparator and using correlation, bias and precision as tools to evaluate the performance of formulas estimating renal function, the CKD-EPI did not show any additional value compared with the MDRD for use in clinical practice. Bias was comparably high for both MDRD and CKD-EPI and both prediction equations had an equal lack of precision: a lack of precision that increased with deteriorating renal function.

The CKD-EPI was developed to overcome the deficiencies of the MDRD equation, such as the lower accuracy at measured GFR >60 ml/min/1.73m^2, and underestimation of eGFR in women and healthy young white men. The proposal by Levey *et al.* to replace the MDRD with the CKD-EPI formula for routine clinical testing because of its superior accuracy can be disputed, for instance in the group of diabetic patients.[14] Although the CKD-EPI performed better than the MDRD in the validation dataset when the GFR was >60 ml/min/1.73m^2, its precision remained limited.[10] As this imprecision was seen in all groups of the validation dataset, transplant status, diabetes, and weight were selected as predictor variables.[11] The performance of the CKD-EPI did not improve significantly as a result of these attempts to improve the precision of the formula. In spite of these findings, this formula is also recommended to be used in diabetic patients. This lack of precision and the presence of bias has consequences for the correct classification of CKD.[14,15]

The performance of the CKD-EPI compared with the MDRD has been sparsely assessed in diabetic patients.[16,17] In these two recent studies, in which diabetic patients with a good renal function[16] or an impaired renal function,[17] respectively, were assessed (mean measured GFR 102±24 ml/min/1.73m^2 using ^{51}CR-EDTA[16] and 55.4±29 ml/min/1.73m^2 using inulin[17]), it was demonstrated that the CKD-EPI had a substantially greater bias than the MDRD. The first study, evaluating the consequences of the bias and imprecision on CKD staging found that 16% of the study population was misclassified as having CKD.[16] Unfortunately, the authors of the first study[16] did not mention the characteristics of the subgroup that was misclassified.

From studies of the general population with middle-aged people it was shown that using the CKD-EPI equation to estimate GFR reduces the number of patients categorised in CKD stage III-V (eGFR <60 ml/min/1.73m^2).[17,18] People who had an MDRD-eGFR <60 ml/min/1.73m^2 but were reclassified to 'normal' (no CKD) using the CKD-EPI, had a cardiovascular risk profile similar to the population without evidence of CKD and had no greater expectation of mortality during follow-up. In both studies the individuals who were reclassified were more often white, women and younger. Those who remained in stage 3a (eGFR <60 and ≥45 ml/min/1.73m^2) had a significantly greater burden of diabetes, higher fasting plasma glucose, and higher HbA1c levels.

Based on the results of our study, it can be suggested that the CKD-EPI might lead to underdiagnosing of kidney disease in younger subjects; overall 19.8% is categorised in a lower stage when the CKD-EPI is used. Although the number of patients included in this study is small, there is a trend for young and especially female patients to be re-categorised in a lower CKD stage when the CKD-EPI is used to estimate GFR. Differences between estimated GFR using the CKD-EPI and MDRD were largest in the age categories <65 years. The fact that the bias of the CKD-EPI and the MDRD is influenced by age was found previously in a group of potential kidney donors and adult patients who underwent a GFR measurement for clinical reasons, using ^{125}I-iothalamate.[19] It was shown that absolute bias was larger in the younger patient group.[19]

From previous studies we know that younger people (18-64 years) have an increased risk of mortality and end-stage renal disease at similar levels of GFR estimated by the MDRD-4.[20] Such a finding in relatively young persons requires further evaluation of the patient. The sooner these people are diagnosed as having a reduced renal function, the sooner they can be treated.

Apart from creatinine-based renal function prediction equations, cystatin C is also increasingly mentioned as a biomarker that can be used in formulas to predict GFR. Various studies found cystatin C to be a better predictor of GFR than creatinine although other studies found no difference.[21-23] Particularly in patients with muscle loss and in populations where rapid detection of small changes in GFR is important, cystatin C may provide a more accurate estimate of kidney function than serum creatinine.[21] In patients with DM, cystatin C appears to be more sensitive than creatinine for the detection of mild reduction in kidney function.[24] However, whether cystatin C improves medical decision making, leading to more favourable patient outcomes, remains to be evaluated in future research.[25]

Strengths and limitations

This is one of the few studies evaluating the effect of the CKD-EPI on the classification of CKD in a diabetic cohort. Due to the wide range of renal function of the included patients, this study gives a good representation of the precision of both GFR-estimating equations in a diabetic population. Recent studies have emphasised the importance of careful calibration of serum creatinine measurements.[26] The fact that a traceable enzymatic serum

creatinine technique was used in this study increases the validity of the study results.

Unfortunately, as we did not have a gold standard to measure GFR, 24-hour CrCl was used as the measurement. Inaccuracies in the 24-hour collection are a concern in general, but in patients with diabetes mellitus, autonomic neuropathy might lead to an inability to completely empty the bladder as well. However, since the CrCl is still the second best and most frequently used measure to assess renal function, comparing the two GFR prediction equations with the 24-hour CrCl is still clinically relevant. We did not have data on urinary protein excretion. Therefore we cannot make inferences about the presence of chronic kidney disease (CKD) other than CKD stage III-V in our population. Moreover, serum creatinine concentrations were measured only once in the majority of people, so we cannot speculate on chronicity of CKD in this population. Still, estimated GFR based on a single creatinine measurement offers reasonable accuracy for identifying CKD stage III or higher.

CONCLUSION

The classification of CKD in diabetic patients and the related risk of complications (i.e. cardiovascular morbidity and mortality, acute kidney injury, end-stage renal disease) can be facilitated by GFR estimations, as long as one recognises that the precision of both the MDRD and the CKD-EPI equations is limited. Compared with the MDRD equation, the CKD-EPI equation gives higher estimates of GFR in young diabetic people, leading to a lower prevalence of CKD on population level. The performance of the CKD-EPI equation in diabetic patients with normal renal function has to be determined in a study in which a gold standard to measure renal function is used as comparator.

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