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Predictive Performance of Renal Function Equations for Patients with Chronic Kidney Disease and Normal Serum Creatinine Levels

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Abstract. Accurate renal function measurements are important for the diagnosis and treatment of kidney disease, proper medication dosing, interpretation of possible uremic symptoms, and decision-making regarding when to initiate renal replacement therapy. Because the use of highly accurate filtration markers to measure renal function has traditionally been limited by cumbersome and costly techniques and the involvement of radioactivity (among other factors), renal function is typically estimated by using specially derived prediction equations. These formulae usually use serum creatinine levels, *i.e.*, a marker of filtration that is insensitive to mild/moderate decreases in GFR. Although attempts have been made to validate certain renal function prediction equations among patients with chronic kidney disease (CKD) with abnormal serum creatinine levels, this is the first study to specifically evaluate the predictive performance of these equations for patients with CKD and serum creatinine levels in the normal range. The results of eight prediction equations for 109 patients with CKD and serum creatinine levels of ≤1.5 mg/dl were compared with standard iohexol GFR values. The most accurate results were obtained with the Cockroft-Gault and Bjornsson equations. The most precise formulae were the Modification of Diet in Renal Disease Study equations, although they were highly biased. Even the most accurate results exhibited levels of error that made them suboptimal for clinical treatment of these patients. These results suggest that measurement of GFR with endogenous or exogenous filtration markers might be the most prudent strategy for the assessment of renal function in the CKD population with normal serum creatinine levels. Further studies are needed to confirm the generalizability of these findings for this patient subgroup.

Identifying and stratifying patients at risk for renal disease are integral parts of clinical nephrology. These tasks are performed in part by measuring the GFR, which is generally considered to be the best marker of renal function in healthy and diseased states (1). The GFR can be precisely measured by using the filtration markers inulin, [^{125}I]iothalamate, ^{51}Cr-ethylenediaminetetraacetic acid, ^{99m}Tc-diethylenetriaminepentaacetic acid, and iohexol (2). However, because these markers are, to varying degrees, costly and cumbersome to use and may involve radioactivity, which necessitates special handling and disposal and limits use, these standard methods of measurement are not typically used in clinical practice.

A far more common method has been to estimate renal function by using specifically designed prediction equations based on demographic characteristics, such as age, gender, race, and weight, and biochemical indices, including serum creatinine, urea, and albumin levels. Of these, probably the most frequently applied formula is that proposed by Cockroft and Gault (3). Regardless of whether these equations were derived to predict creatinine clearance (3–8) or GFR (9,10), they all use and are influenced by the serum creatinine level. Serum creatinine levels are greatly dependent on dietary intake, total muscle mass, the use of certain medications that can interfere with renal creatinine handling, and renal and extrarenal excretion, all of which might be altered in chronic kidney disease (CKD) (11). In fact, serum creatinine levels can be insensitive markers of true renal function in CKD. One study assessing the reliability of filtration markers in CKD noted that a >50% reduction in glomerular ultrafiltration needed to occur before the serum creatinine level increased above normal levels (defined as serum creatinine levels of >1.4 mg/dl) (12). Therefore, many patients with CKD maintain serum creatinine levels in the normal range despite having significantly impaired renal function.

Although previous studies focused on validating these prediction equations among patients with elevated serum creatinine levels and in other subpopulations (9,13-15), these equations have not been tested in a CKD population with normal-range serum creatinine levels. This study aimed to address this issue by comparing the results of renal function prediction equations with iohexol GFR measurements (16) for a population of subjects with documented CKD and serum creatinine levels of ≤1.5 mg/dl.

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Materials and Methods

A detailed description of the CKD cohort used in this study was provided elsewhere (17). All recruited patients were examined at least once during 1997, in one of eight nephrology departments in Germany, Austria, or South Tyrol. Subjects were Caucasian patients between the ages of 19 and 65 yr who were examined for evaluation or treatment of manifestations of kidney disease, such as proteinuria, active urinary sediment, or anatomic kidney abnormalities. Of the 227 patients in the original study, here we included only 109 who exhibited serum creatinine levels of ≤1.5 mg/dl. These subjects demonstrated the following primary CKD diagnoses: glomerulonephritis, $n = 64$ (58.7%); polycystic kidney disease, $n = 9$ (8.3%); pyelonephritis, $n = 6$ (5.5%); other, $n = 19$ (17.4%); unknown, $n = 11$ (10.1%). The majority (93%) of the 227 patients who were originally diagnosed as having glomerulonephritis demonstrated biopsy-proven disease. Exclusion criteria included diabetes mellitus, malignancies, liver, thyroid, or infectious diseases at the time of recruitment, organ transplantation, allergies against ionic contrast media, and pregnancy.

Serum and ethylenediaminetetraacetic acid-treated plasma were promptly separated from whole blood that had been collected after an overnight (12-h) fast and were frozen at −80°C before analysis. Serum albumin levels were measured with the bromocresol green method, using a kit obtained from Boehringer Mannheim (Mannheim, Germany). Serum creatinine levels were determined with the Jaffe method adapted for autoanalyzers. All laboratories were subject to external quality control assessments, and results were well within the serum creatinine concentration limits dictated by regulatory agencies [*i.e.*, precision coefficients of variation (CV) of <6% for repeated measurements and accuracies of <10%]. Depending on the serum creatinine level, two or three blood samples were collected for determination of the true GFR (expressed as milliliters per minute per 1.73 m^2) with the plasma iohexol clearance method, as described by Gaspari *et al.* (16). Between- and within-run CV for the key analytes (*i.e.*, iohexol and urinary protein levels) were consistent with data reported elsewhere (16,18,19). Specifically, CV for all assays were between 5 and 10%.

Predicted renal function was calculated by using eight previously published equations (3–10). All except the Modification of Diet in Renal Disease (MDRD) Study equations (9,10), which measure GFR, were originally designed to calculate creatinine clearance. The cutoff level for serum creatinine concentrations was defined *a priori* as ≤1.5 mg/dl, because this value is at or slightly above the upper limit for most clinical laboratories.

The accuracy of prediction equations includes components of bias and precision. Bias is any systematic nonrandom deviation causing a prediction error and was calculated as the mean prediction error (*ME*) (20), which was defined as

$$ME = \frac{1}{N}\sum_{i=1}^{N}(pe_i)$$

where pe_i is the predicted value − the true value.

The precision of equations is assessed on the basis of the degree of spread of the series of observations and is reflected by the amount of expected variation in the estimates. This is measured with the R^2 statistic, which indicates the overall fit of the model (21). The accuracy of each equation, or how well it represents the true renal function, was assessed by comparing its results with those of the standard method (in this case, the iohexol GFR). This was performed by using the following equation: [predicted value − true value (*i.e.*, iohexol measurement)] × 100/iohexol measurement. For each equation, the number of subjects with predicted GFR values within 30 or 50% of the iohexol GFR was then tallied.

Results

The eight renal function equations evaluated are listed in Table 1; all equations use serum creatinine levels to predict renal function. Most of the study subjects were male and all were Caucasian, between the ages of 18 and 64 yr, as indicated in Table 2. The geometric mean serum creatinine level was 1.2 mg/dl, with no values higher than 1.5 mg/dl. The majority of patients exhibited proteinuria (microproteinuria to nephrotic-range proteinuria). Twenty-seven of the 109 subjects (25%) exhibited iohexol GFR values of <80 ml/min per 1.73 m^2, despite demonstrating normal-range serum creatinine levels.

The predictive performance of the equations is presented in Table 3. Precision, as reflected by the statistic R^2, was greatest for the MDRD 1, MDRD 2, Jelliffe 1, and Jelliffe 2 equations. Bias, as indicated by the mean prediction error, was greatest for the MDRD 1, MDRD 2, Jelliffe 1, Jelliffe 2, and Gates equations. The most accurate results were obtained with the Bjornsson and Cockroft-Gault equations; results were within 30% of the iohexol GFR in 62 and 59% of the cases and within 50% of the iohexol GFR in 89 and 88% of the cases, respectively.

Discussion

Accurate assessment of renal function among patients with CKD is important for diagnostic and interventional purposes, proper medication dosing, interpretation of symptoms that might be uremic in nature, and decision-making regarding when the initiation of dialysis might be appropriate. Because of the numerous disadvantages of using filtration markers, derived prediction equations are typically used, throughout the world, to estimate renal function (3–10). Although some of the equations have been validated in CKD populations with clearly elevated serum creatinine levels (9,14), this is the first attempt to estimate their predictive performance for subjects with CKD and serum creatinine levels within the normal range. Why is this important? A significant subset of patients are referred for evaluation simply on the basis of abnormal urinary sediments (*e.g.*, cellular casts or hematuria), proteinuria, or anatomic disease (*e.g.*, renal cysts or cortical thinning). It is not uncommon for these patients to exhibit serum creatinine levels in the normal range, simply because of the limited sensitivity of serum creatinine measurements in detecting GFR decreases (12). Clinicians then typically base their assessments of renal function on formulae that rely heavily on serum creatinine levels for their predictive capabilities and that have not been validated for this particular subpopulation. It was this practice that we wanted to assess.

The most accurate renal function estimates were derived by using the Cockroft-Gault and Bjornsson equations, with approximately 60% of their results being within 30% and 90% being within 50% of the true GFR (as measured with the iohexol clearance technique). In some respects, it is reassuring that the most commonly used equation (*i.e.*, the Cockroft-Gault equation) is at least as good as the others in terms of its

Table 1. GFR prediction equations[a]

Cockroft-Gault[b]	$\frac{(140 - age) \times weight}{72 \times S_{cr}}$ ($\times$ 0.85 if female)
MDRD 1[c]	$170 \times S_{cr}^{-0.999} \times age^{-0.176} \times$ (0.762 if female) $\times$ (1.180 if black) $\times S_u^{-0.170} \times Alb^{+0.318}$
MDRD 2[c]	$186 \times S_{cr}^{-1.154} \times age^{-0.203} \times$ (1.212 if black) $\times$ (0.742 if female)
Jelliffe 1[b,d]	$\frac{98 - 0.8 \times (age - 20)}{S_{cr}}$ ($\times$ 0.90 if female)
Jelliffe 2[b]	Male: $100/S_{cr} - 12$
	Female: $80/S_{cr} - 7$
Mawer[b]	Male: $\frac{weight \times [29.3 - (0.203 \times age)] \times [1 - (0.03 \times S_{cr})]}{(14.4 \times S_{cr}) \times (70/weight)}$
	Female: $\frac{weight \times [25.3 - (0.175 \times age)] \times [1 - (0.03 \times S_{cr})]}{(14.4 \times S_{cr}) \times (70/weight)}$
Bjornsson[b]	Male: $\frac{[27 - (0.173 \times age)] \times weight \times 0.07}{S_{cr}}$
	Female: $\frac{[25 - (0.175 \times age)] \times weight \times 0.07}{S_{cr}}$
Gates[b]	Male: $(89.4 \times S_{cr}^{-1.2}) + (55 - age) \times (0.447 \times S_{cr}^{-1.1})$
	Female: $(60 \times S_{cr}^{-1.1}) + (56 - age) \times (0.3 \times S_{cr}^{-1.1})$

[a] S_{cr}, serum creatinine level (mg/dl); S_u, serum urea level (mg/dl); Alb, serum albumin level (g/dl); BSA, body surface area; age, in years; weight, in kilograms; MDRD, Modification of Diet in Renal Disease.
[b] Creatinine clearance measurement (ml/min).
[c] GFR measurement (ml/min per 1.73 m^2).
[d] Times body surface area/1.73 m^2.

predictive capability. These data, however, are also disquieting. They suggest that, even with the most accurate predictions, four of 10 patients would demonstrate predicted renal function at least 30% higher or lower than actual renal function. What are the clinical implications of these results? Let us suppose that a patient exhibits a serum creatinine level of 1.2 mg/dl and CKD has been diagnosed on the basis of proteinuria and cellular casts. Let us also presume that the actual GFR is 80 ml/min per 1.73 m^2. If any of these prediction equations are used to estimate renal function, then there is a $\geq$40% chance that the prediction would be $<$56 or $>$104 ml/min per 1.73 m^2.

Of note, the accuracy of each equation must also be understood in the context of both its precision and its bias. Precision is based on the overall spread of the observations (the smaller the spread, the greater the precision). Bias is a systematic deviation that may cause typical predictions to be either too high or too low. Bias varies of course, depending on the circumstances under which the measurements are made. For example, one potential source of bias involves the well documented differences among laboratories in the calibration of assays used to measure serum creatinine levels (22). Because the creatinine level is a heavily weighted variable in most of these equations, these differences would affect prediction results. However, because bias is a systematic deviation, it can be corrected for with correction factors that are multiplied by the prediction formula results. Poor precision cannot be corrected for in this manner, however. The use of these correction factors can potentially improve the accuracy of the formulae, particularly if their precision is high (*e.g.*, the MDRD Study equations). The issue of how to improve the overall accuracy of these prediction equations then arises. It is obviously not feasible to derive a specific correction factor for each equation in each laboratory. Standardization of the calibration of creatinine measurements in all laboratories can be considered, but this would require much time and effort. Furthermore, even this step would not remove other sources of bias.

An alternative strategy would be to use other, more accurate, renal function markers for these particular patients with CKD. Endogenous filtration markers, such as cystatin C (a protein that is produced by nucleated cells at a constant rate and is then

Table 2. Patient characteristics

n	109
Age (yr)	43 ± 13[a] (18 to 64)[b]
Gender (% men)	77 ± 70.6
Caucasian (%)	100
Weight (kg)	76[c] (66 to 85)[d]
Creatinine level (mg/dl)	1.2[e] (1.0 to 1.3)[d]
Urea level (mg/dl)	33[c] (21 to 42)[d]
Albumin level (g/dl)	4.6[c] (4.3 to 4.9)[d]
Proteinuria (g/24 h)	0.471[e] (0.157 to 1.27)[d] (0.000 to 8.340)[b]
GFR[f] (ml/min per 1.73 m^2)	109[c] (88 to 138)[d] (18 to 205)[b]

[a] Mean ± SD.
[b] Complete range.
[c] Median.
[d] 25th to 75th percentile range.
[e] Geometric mean.
[f] Measured with the iohexol clearance method.

filtered by glomeruli), do exist. Cystatin C measurements have been observed to be more closely correlated with GFR (23–25) and better able to detect mild reductions in GFR, compared with serum creatinine levels (26,27). However, the superiority of cystatin C measurements has not been formally validated in a population with documented CKD and normal serum creatinine levels. Alternatively, the use of highly accurate, exogenous renal filtration markers, whose application has traditionally been limited by cumbersome technique, expense, and radioactivity (among other factors), can be considered (2). In the past decade, a renal filtration marker without many of these limitations has gained prominence. Iohexol is a contrast agent that has been very well correlated with standard GFR markers (28,29); it is relatively inexpensive, nonradioactive (28), and safe to use in special patient populations, including those with severe renal insufficiency (30,31). Its ease of use is notable, because no urine samples are needed and, for patients with GFR of >40 ml/min per 1.73 m^2, only one plasma sample (obtained a few hours after the iohexol injection) is required (32). Determination of true GFR with iohexol measurements might thus be an accurate, inexpensive, safe, and relatively easy method to apply to the CKD population with normal serum creatinine levels.

Table 3. Bias, precision, and accuracy of renal function equations

Renal Function Equations	Precision[a]	Bias[b]	Accuracy (% within Specified Range of Iohexol GFR)	
			30%	50%
Cockroft-Gault	0.17	−26.5	59	88
MDRD 1	0.31	−46.0	24	71
MDRD 2	0.29	−41.7	28	82
Jelliffe 1	0.28	−43.3	30	77
Jelliffe 2	0.26	−39.8	36	82
Mawer	0.04	−15.2	53	80
Bjornsson	0.17	−23.9	62	89
Gates	0.24	−38.6	35	86

[a] As assessed with the R^2 statistic.
[b] As assessed with the mean prediction error. ml/min per 1.73 m^2.

The generalizability of our results is limited by the fact that no diabetic, black, or very elderly subjects were included in the study population. Additionally, the equations studied were meant to predict either GFR or creatinine clearance. Because of concerns that creatinine clearance assessments systematically overestimate GFR, some researchers comparing the two have adjusted the creatinine clearance equations to correct for bias (9). However, because the two types of equations are often used interchangeably in general clinical practice to assess "renal function," we decided against this adjustment.

In conclusion, our analysis of the predictive performance of renal function equations for a CKD population with normal serum creatinine levels demonstrated that the most accurate results were obtained with the Cockroft-Gault equation, whereas the most precise formula was the MDRD Study equation. Unfortunately, the predictive capabilities of these formulae were suboptimal for ideal patient care. These results suggest that direct measurements of renal function, using either endogenous or exogenous filtration markers, might be the best way to consistently obtain accurate assessments of renal function for these patients. Further studies are needed to confirm the generalizability of our findings for this common subgroup of patients.

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