Creatinine Production, Nutrition, and Glomerular Filtration Rate Estimation

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Abstract. This study examined the validity and clinical implications of the assumption of the Modification of Diet in Renal Disease Study (MDRD) formula that age, gender, race, and BUN account for creatinine production (CP). The relationships of MDRD GFR, CP, and nutrition were examined in 1074 Dialysis Morbidity and Mortality Study Wave II patients with reported measured creatinine clearances at initiation of dialysis. Age, gender, race, BUN, and serum creatinine (Scr) were used to calculate MDRD GFR. The measured 24-h urinary creatinine was used to estimate CP. In linear regression, Scr positively correlated with CP independent of age, gender, race, and BUN. Compared with the highest CP quartile, the lowest CP quartile had lower creatinine clearance (5.8 ± 2.9 *versus* 11.3 ± 3.4 ml/min, $P < .01$) despite lower Scr (5.8 ± 2.6 *versus* 8.6 ± 3.1 mg%, $P < .01$). There was an excellent correlation between the reciprocal of Scr and the MDRD GFR ($r = 0.90$). As a result, the MDRD GFR was higher in the lowest CP quartile (10.9 ± 4.6 *versus* 7.6 ± 2.4 ml/min, $P < .01$). Malnutrition (48% *versus* 26%, $P < .01$) was more common in the lowest CP quartile. Each 5-ml/min increase in MDRD GFR was associated with 21% higher odds of malnutrition ($P = 0.046$) in a multivariable logistic regression, which was abolished by controlling for CP. The fundamental assumption of the MDRD formula is invalid in patients with advanced renal failure, and the use of this formula in these patients might introduce biases.

Serum creatinine (Scr) level is a function of creatinine production and renal excretion. Age, gender, race, and blood urea nitrogen (BUN) are unlikely to fully account for creatinine production. However, the Modification of Diet in Renal Disease Study (MDRD) equation that relies on age, gender, race, BUN, and serum creatinine to estimate the GFR implicitly assumes that age, gender, race, and BUN account for creatinine production (1). If this assumption is not valid, then the MDRD estimate of GFR in patients with low and high creatinine production will be invalid, as Scr is the most important predictor variable in the MDRD formula accounting for 80.4% of the variability in estimated GFR (2). The validity of this assumption, hence the applicability of the MDRD formula, has not been rigorously tested in patients with advanced renal failure.

The hypothesized associations of nutritional status and creatinine production with MDRD formula estimate of GFR are as follows. In malnourished patients with low muscle mass and low creatinine production, the Scr at initiation of dialysis will be low. If age, sex, race and BUN do not fully account for creatinine production and the MDRD estimate of GFR is inversely proportional to Scr, the MDRD GFR will be expected to be higher than the measured creatinine clearance in patients with low creatinine production. For the same reasons, in patients with high creatinine production, the MDRD GFR will be lower than the measured creatinine clearance. The overestimation of GFR in patients with low creatinine production (malnourished patients) and *vice versa* in patients with high creatinine production (well-nourished patients) might result in a spurious association of higher prevalence of malnutrition in patients with higher MDRD GFR compared with those with lower MDRD GFR. We examined this hypothesis in the Dialysis Morbidity Mortality Study (DMMS) Wave II patients with measured creatinine clearances reported in the Medical Evidence form.

Materials and Methods

The USRDS DMMS II is a prospective registry of a national, random sample of incident chronic hemodialysis and peritoneal dialysis patients who initiated dialysis therapy in 1996 and early 1997 in the United States (3–5). Patients with invalid study start dates, missing USRDS identification numbers, duplicate entries, age <18 yr, and previous renal replacement therapy were excluded. Of these, DMMS II patients with measured creatinine clearance reported in the Medical Evidence form and with non-missing data for age, gender, race, height, weight, BUN, Scr, and albumin were included in the analysis.

The DMMS II patient questionnaire data on demographics (age, gender, and race), cause of ESRD (diabetes or others), insurance

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status (Medicare or non-Medicare), comorbid conditions (coronary artery disease, cerebrovascular disease, peripheral vascular disease, congestive heart failure, malignancy, acquired immunodeficiency syndrome, chronic lung disease, and left ventricular hypertrophy), smoking, height, weight, and clinical diagnosis of malnutrition as determined by the dialysis unit personnel, and functional ability were used in this analysis (3–5). Medical Evidence form data on BUN, Scr, serum albumin, and 24-h creatinine clearance were also used (6).

Calculations for GFR and Creatinine Production

The Modification of Diet in Renal Disease Study (MDRD) equation [GFR = 270 × (Scr − 1.007) × (age − 0.18) × 0.775 if female × 1.18 if black × (BUN − 0.169)] was used to determine GFR values at the initiation of dialysis therapy (1,2,7). The measured 24-h urinary creatinine (g/d) was considered indicative of creatinine production and was calculated on the basis of the measured creatinine clearance and Scr reported in the Medical Evidence form as [creatinine clearance (ml/min) × Scr (mg/dl)]/70. Four creatinine production groups were defined by urinary creatinine quartiles.

Malnutrition was defined as a clinical diagnosis of malnutrition as recorded by dialysis unit personnel or serum albumin 2.9 g/dl (25^{th} percentile) or BMI ≤ 19.2 kg/m^2 (10^{th} percentile). As lower BMI might reflect a muscular but thin individual, a stringent threshold for BMI was used to increase the specificity of BMI criteria for malnutrition.

The USRDS_ID variable enabled the linkage of Wave 2 data to other USRDS files (8). The treatment history, claims, and patients files provided data on follow-up periods, mortality, and transplantation (8). Patients were tracked until loss to follow-up, transplantation, death, or December 31, 1998.

Statistical Analyses

The differences in demographics, comorbidity, nutritional status, and functional status of DMMS patients with and without reported creatinine clearances were examined by χ^2 tests or ANOVA as appropriate. Linear regression was used to examine the association of creatinine production, age, gender, race, and BUN with Scr levels. The relationship of MDRD GFR with the reciprocal of Scr was examined graphically and by Pearson correlation. The MDRD GFR minus the measured creatinine clearances was plotted against creatinine production.

Paired groups *t* tests were used to compare MDRD GFR and measured creatinine clearances within each of the creatinine production quartiles. The differences in baseline characteristics, nutritional status, and subsequent death and transplantation among creatinine production quartiles were examined by χ^2 tests for trends or ANOVA to examine the biologic relevance of creatinine production.

A forward stepwise logistic regression model of demographics, cause of ESRD (diabetes or others), insurance status (Medicare or non-Medicare), comorbid conditions, and smoking history was used to identify factors independently associated with malnutrition at the initiation of dialysis. The association of MDRD GFR with malnutrition was examined by adding the MDRD GFR into the multivariable logistic regression model with and without measured 24-h urinary creatinine.

Results

Of the 4024 patients in the DMMS II, 229 were excluded as per exclusion criteria. Of the remaining 3795 patients, 1356 had measured creatinine clearances reported in Form 2728. Compared with those without reported creatinine clearances, patients with reported creatinine clearances were older (62 ± 15 yr *versus* 57 ± 16 yr, $P < 0.001$), less likely to be men (47% *versus* 56%, $P < 0.001$) or African-American (23% *versus* 31%, $P < 0.001$) and more likely to have Medicare insurance (58% *versus* 46%, $P < 0.001$). These patients had significantly ($P < 0.001$) increased prevalence of coronary artery disease (43% *versus* 34%), congestive heart failure (39% *versus* 30%), peripheral vascular disease (21% *versus* 17%), and left ventricular hypertrophy (23% *versus* 18%). Inability to ambulate independently (14% *versus* 11%, $P = 0.018$) and inability to transfer independently (12% *versus* 9%, $P = 0.002$) were also more common. Body mass index (25.6 ± 5.6 kg/m^2 *versus* 26.1 ± 5.8 kg/m^2, $P = .018$), BUN (86 ± 30 mg/dl *versus* 96 ± 32 mg/dl, $P < 0.001$) and Scr (6.9 ± 2.9 mg/dl and 9.5 ± 3.6 mg/dl, $P < 0.001$) were lower in those with reported creatinine clearances.

Of the 1356 patients with reported creatinine clearances, 1074 patients had non-missing data for age, gender, race, height, weight, BUN, Scr, and albumin and were further studied. Baseline clinical characteristics, nutritional and renal parameters, and outcomes in creatinine production quartiles are summarized in Table 1. Scr levels were higher in patients with higher creatinine production (Table 1). In a multivariable linear regression, this association was independent of age, gender, race, and BUN (Table 2). Despite lower Scr levels, the estimated creatinine clearances of low creatinine producers were lower than those of high creatinine producers (Table 1).

There was an excellent correlation of the MDRD GFR values with the reciprocal of Scr (Pearson $r = 0.90$). Because of the strong inverse association of MDRD GFR with Scr and because the association of creatinine production with Scr was independent of age, gender, race, and BUN, in patients with low creatinine production (and therefore low Scr) MDRD GFR values are expected to be high. Indeed, as shown in Table 1 and Figure 1, the MDRD GFR values were higher than the measured creatinine clearances in patients with low creatinine production. In patients with high creatinine production (and therefore high Scr), MDRD GFR values are expected to be low. Indeed, in these patients, the MDRD GFR values were lower than those of the creatinine clearances (Table 1 and Figure 1).

The biologic relevance of creatinine production is shown in Table 1. Patients with lower creatinine production were older, more likely to be women, and had significantly more atherosclerotic diseases, congestive heart failure, left ventricular hypertrophy, and worse functional status (Table 1). Not surprisingly, patients with lower creatinine production had lower BMI and serum albumin and higher prevalence of clinical diagnosis of malnutrition (Table 1). More importantly, patients with lower creatinine production had higher proportion of deaths and lower proportion of transplants (Table 1).

In a multiple logistic regression model, inability to independently eat or ambulate, AIDS, and congestive heart failure were independently associated with malnutrition. When the MDRD GFR was added into the model, each 5-ml/min increase in GFR was associated with 21% higher odds of malnutrition ($P = 0.046$) (Table 3). However the association of

Table 1. Baseline patient characteristics and subsequent outcomes by creatinine production quartiles

	1st Quartile UCR < 0.57 (n = 272)	2nd Quartile 0.57 ≤ UCR < 0.78 (n = 266)	3rd Quartile 0.78 ≤ UCR < 1.00 (n = 262)	4th Quartile ≥ 1.00 (n = 274)	P value
Demographics					
age, mean ± SD, yr	66 ± 14	64 ± 14	62 ± 14	56 ± 15	<0.001
male gender, *n* (%)	111 (41)	93 (35)	122 (47)	182 (66)	<0.001
African-American ethnicity, *n* (%)	66 (24)	56 (21)	59 (23)	78 (28)	0.223
Medicare insurance, *n* (%)	190 (70)	167 (63)	147 (56)	114 (42)	<0.001
Comorbid conditions					
diabetes cause of renal failure, *n* (%)	125 (46)	118 (44)	111 (42)	132 (48)	0.722
coronary artery disease, *n* (%)	135 (50)	119 (45)	116 (44)	97 (35)	0.001
congestive heart failure, *n* (%)	136 (50)	99 (37)	104 (40)	84 (31)	<0.001
cerebrovascular accident, *n* (%)	43 (16)	31 (12)	37 (14)	30 (11)	0.182
peripheral vascular disease, *n* (%)	72 (26)	57 (21)	51 (19)	39 (14)	<0.001
left ventricular hypertrophy, *n* (%)	78 (29)	57 (21)	71 (27)	49 (18)	0.019
smoker within past year, *n* (%)	94 (35)	85 (32)	101 (39)	101 (37)	0.304
AIDS, *n* (%)	3 (1.1)	2 (.8)	1 (.4)	7 (2.6)	0.174
Functional status					
requires assistance to eat, *n* (%)	12 (4)	3 (1)	7 (3)	4 (1)	0.077
requires assistance to transfer, *n* (%)	56 (21)	31 (12)	24 (9)	15 (5)	<0.001
Nutritional parameters					
body mass index, mean ± SD	24.5 ± 5.7	25.3 ± 5.8	26.0 ± 5.7	26.5 ± 5.1	<0.001
serum albumin, mean ± SD, g/dl	3.2 ± 0.7	3.3 ± 0.6	3.3 ± 0.6	3.4 ± 0.7	<0.001
malnutrition[a], *n* (%)	130 (48)	90 (34)	83 (32)	72 (26)	0.001
Renal function parameters					
blood urea nitrogen, mean ± SD, mg/dl	87.0 ± 30.8	83.5 ± 30.3	84.0 ± 28.5	89.6 ± 30.3	0.062
serum creatinine, mean ± SD, mg/dl	5.8 ± 2.6	6.3 ± 2.2	6.7 ± 1.9	8.6 ± 3.1	<0.001
MDRD GFR, mean ± SD, ml/min[b]	10.9 ± 4.6	9.5 ± 3.3	8.9 ± 2.8	7.6 ± 2.4	<0.001
creatinine clearance, mean ± SD, ml/min[b]	5.8 ± 2.9	8.3 ± 2.4	9.8 ± 2.7	11.3 ± 3.4	<0.001
urine creatinine, mean ± SD, g/24 h	0.42 ± 0.13	0.68 ± 0.06	0.88 ± 0.06	1.32 ± 0.34	
Outcomes during follow-up					
transplantation, *n* (%)	13 (5)	13 (5)	23 (9)	49 (18)	<0.001
death, *n* (%)	153 (56)	132 (50)	110 (42)	66 (24)	<0.001

[a] Malnutrition was defined as the presence of clinical diagnosis of malnutrition, serum albumin ≤25th percentile (≤2.9), or body mass index ≤10th percentile (≤19.25).

[b] Within each creatinine production quartile, MDRD GFR was significantly different from creatinine clearance using a paired *t* test ($P < 0.001$).

MDRD GFR with malnutrition was no longer significant with further addition of creatinine production into the model (Table 3). On the other hand, creatinine production had an independent negative association with malnutrition (Table 3).

Discussion

The validity and applicability of the MDRD formula and other estimates of GFR has been a matter of considerable debate (9–11). The results of this study show that as the MDRD formula estimate of GFR does not accurately account for creatinine production in patients with advanced kidney disease, the interpretation of clinical outcomes using MDRD GFR could introduce biases. On the basis of the multivariable model in Table 3, which does not include total urinary creatinine excretion, it might be concluded that patients with relatively low Scr levels and high MDRD GFR were initiated on dialysis earlier because they had malnutrition, while in fact, higher MDRD GFR in patients with malnutrition was the result of overestimation of GFR by the MDRD formula in malnourished patients with lower Scr levels.

Although true GFR (*e.g.* iothalamate or iohexol clearances) was not directly measured in this retrospective study, the fundamental assumptions underlying the MDRD equation were critically examined. If the fundamental assumptions of the MDRD formula are invalid in the extremes of creatinine production, GFR estimations by the MDRD formula in patients with low and high creatinine production are likely to be invalid. As creatinine clearance overestimates true GFR, it is quite likely that the actual GFR of the lowest creatinine production quartile was even lower than the measured creatinine clearance of 5.8 ml/min and not the 10.9 ml/min estimated by the MDRD formula (Table 1). The MDRD formula implies

Table 2. Multiple linear regression model of serum creatinine ($n = 1074$)

Dependent Variable: log serum creatinine[a]	Regression Coefficient	Standard Error	Adjusted $R^2 = 0.36$	
Independent Variables			Standardized Regression Coefficient	*P* Value
Log 24-h urine creatinine[a]	0.254	0.019	0.345	<0.001
Log blood urea nitrogen[a]	0.321	0.026	0.307	<0.001
Age, yr	−0.005	0.0006	−0.216	<0.001
African-American ethnicity	0.160	0.021	0.188	<0.001
Male gender	0.057	0.018	0.079	0.002
Constant	0.788	0.119	—	<0.001

[a] Natural logarithm transformations used to satisfy the linearity and homoscedasticity assumptions of linear regression.

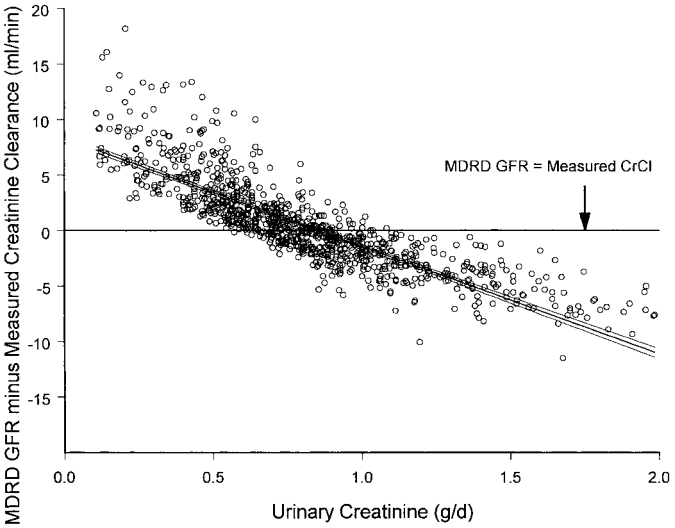

Figure 1. Plot of difference between Modification of Diet in Renal Disease Study (MDRD) GFR and measured creatinine clearances against creatinine production estimated by creatinine excretion.

that all patients of a given age, gender, race, BUN, and Scr have the same GFR. For example, in two 65-yr-old white women with BUN of 70 mg% and Scr of 5 mg%, the GFR calculated by the MDRD formula will be the same (9.3 ml/min), even if the 24-h urinary creatinine excretion is 0.5 g/d in one and 1.5 g/d in another.

The MDRD formula has not been validated with true GFR measurements in patients with advanced renal failure and, more specifically, in patients at extremes of creatinine production. The National Kidney Foundation guidelines recommend that measuring 24-h creatinine clearance to assess GFR is not more reliable than estimating GFR from a prediction equation (1). However, these guidelines also state that important exceptions include estimation of GFR at initiation of dialysis and in individuals with variation in dietary intake or muscle mass, as these factors are not specifically taken into account in GFR prediction equations. Nonetheless, it has been suggested that the GFR prediction equations be used to accurately time the initiation of renal replacement therapy (12). In addition, the MDRD estimate is also used by the United States Renal Data System to calculate GFR at the initiation of dialysis (13).

In the African American Study of Kidney Disease and Hypertension (AASK), the correlation of creatinine clearance with GFR determined by iothalamate clearance was quite low ($R^2 = 0.59$) (12). Because of tubular secretion, creatinine clearance consistently overestimates true GFR; it would therefore be expected that the correlation coefficient of creatinine clearance with true GFR would be low. In the MDRD study, when creatinine clearance was corrected for overestimation of GFR by multiplying creatinine clearance by 0.81, the correlation coefficient of the corrected creatinine clearance with iothalamate clearance was quite high ($R^2 = 0.87$) (2).

The error in estimation of true GFR from creatinine clearance is likely consistent overestimation of GFR regardless of the magnitude of creatinine production, as estimation of creatinine clearance accounts for creatinine production but not tubular secretion. On the other hand, the MDRD GFR overestimates GFR in patients with low creatinine production and underestimates GFR in patients with high creatinine production. Thus, misclassification bias for early *versus* late initiation of dialysis is greater with the MDRD estimate than with creatinine clearance. Therefore, the present results support the National Kidney Foundation recommendation to use creatinine clearance to guide the initiation of dialysis (1), as the use of MDRD estimate of GFR at initiation of dialysis might result in biases.

One of the major issues with the measurement of creatinine clearance is the accuracy of the 24-h urine collection (12). Inaccurate 24-h urine collection will bias against finding biologically plausible associations of creatinine production with baseline characteristics and subsequent outcomes. There are several reasons to believe that the 24-h urine collections reported in the Medical Evidence form were reliable. First, as would be expected, patients with lower creatinine production were older, had more comorbidity, and worse functional status. Second, the measured Scr levels were lower in patients with measured lower creatinine production. Finally, if the 24-h urinary collection were inadequate, creatinine production would not be strongly associated with subsequent transplantation and

Table 3. Factors associated with malnutrition[a] in multivariable logistic regression models ($n = 1074$)

Independent Variables[b]	Measured 24-h Urine Creatinine Excluded from Model			Measured 24-h Urine Creatinine Included in Model		
	Odds Ratio	95% CI	*P* value	Odds Ratio	95% CI	*P* value
MDRD GFR (each 5 ml/min increase)	1.21	1.00 to 1.45	0.046	1.08	0.89 to 1.32	0.416
Measured 24-h urine creatinine (each g/d increase)	—	—	—	0.49	0.33 to 0.73	0.001
Require assistance to eat	3.72	1.40 to 9.85	0.008	3.79	1.43 to 10.04	0.007
Require assistance to ambulate	1.81	1.22 to 2.66	0.003	1.62	1.09 to 2.39	0.017
AIDS	13.57	2.94 to 62.62	0.001	14.90	3.21 to 69.29	0.001
Congestive heart failure	1.66	1.27 to 2.16	<0.001	1.61	1.23 to 2.10	0.001

[a] Malnutrition was defined as the presence of clinical diagnosis of malnutrition, serum albumin ≤25th percentile (≤2.9), or body mass index ≤10th percentile (≤19.25).

[b] Variables considered for model that fell out as nonsignificant were: age, gender, race, Medicare insurance, coronary artery disease, cerebrovascular disease, peripheral vascular disease, malignancy, lung disease, require assistance to transfer, left ventricular hypertrophy, diabetes as cause of renal failure, and smoking.

death, and controlling for urinary creatinine would not abolish the association of higher MDRD GFR with malnutrition.

It has been suggested that as much as two thirds of total daily creatinine excretion can occur by extrarenal excretion in patients with advanced renal failure (14). However, our data suggest that 24-h urinary creatinine excretion strongly correlated with malnutrition (Table 3). These findings in incident dialysis patients are similar to the earlier findings by Ohkawa *et al.* (15) that malnutrition strongly correlated with thigh muscle mass quantified by computed tomography and creatinine production (determined from the sum of creatinine present in the spent dialysate and estimated metabolic degradation) in anuric hemodialysis patients. Therefore, even in patients with advanced renal failure, 24-h urinary creatinine excretion is likely an accurate reflection of muscle mass and creatinine generation.

Only about a third of patients initiated on dialysis had creatinine clearances reported. These patients were older and had more comorbidity and worse functional and nutritional status compared with those without reported creatinine clearances. However, the anticipated doubling of the US ESRD population over the next decade will primarily be due to older patients with significant comorbidity (13). Therefore, the results of this study should be generalizable to a large proportion of the rapidly growing segment of the US ESRD population. On the other hand, the MDRD equation was derived and validated in the MDRD cohort with a mean age of 51 ± 13 yr and only 3% diabetes (2,16). This equation was also validated in the AASK population with a mean age of 54 ± 10 yr, 100% African-Americans, and 0% diabetes (12). Therefore, the MDRD and AASK populations are very different from the USRDS DMMS II population, a nationally representative sample of incident dialysis patients. Thus the applicability of a formula derived with regression techniques in a very different population to patients with advanced renal failure is questionable.

There are several limitations to our study. First, the limitations of this study include those of all retrospective observational studies that rely on existent databases. Second, as noted above, only a third of patients had reported measured creatinine clearances, and this might limit the generalizability. Third, the associations noted might be biased by the differential exclusion (due to nonavailability of data) of patients characterized by levels of Scr and/or creatinine production.

We conclude that the assumptions of the MDRD estimate of GFR are invalid in patients with advanced renal failure with high and low creatinine production. These result in a spurious association of malnutrition with higher MDRD GFR. Thus, the application of MDRD formula in patients with advanced renal failure introduces biases. In these patients, creatinine clearance or other measurement techniques should be used instead to estimate GFR.

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