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Prediction of Creatinine Clearance from Serum Creatinine[1]

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Abstract. A formula has been developed to predict creatinine clearance (C_{cr}) from serum creatinine (S_{cr}) in adult males:

$$C_{cr} = \frac{(140 - \text{age})\,(\text{wt kg})}{72 \times S_{cr}\,(\text{mg}/100\,\text{ml})}$$

(15% less in females). Derivation included the relationship found between age and 24-hour creatinine excretion/kg in 249 patients aged 18–92. Values for C_{cr} were predicted by this formula and four other methods and the results compared with the means of two 24-hour C_{cr}'s measured in 236 patients. The above formula gave a correlation coefficient between predicted and mean measured C_{cr}'s of 0.83; on average, the difference between predicted and mean measured values was no greater than that between paired clearances. Factors for age and body weight must be included for reasonable prediction.

It is useful to be able to quickly predict creatinine clearance (C_{cr}) without collecting urine, particularly when instituting therapy with potentially toxic drugs which are primarily excreted by the kidneys. Several formulae [1–3] and a nomogram [4, 5] have been reported to give satisfactory results. Serum creatinine (S_{cr}), body weight, age and sex are variables which have been utilized to predict C_{cr}.

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We have derived a simple formula for predicting C_{cr} from serum creatinine, age and body weight and have compared its ability to predict C_{cr} with that of previously reported methods [1–4] in 236 patients. We also compared the variation between values for predicted and measured C_{cr} with the variation found between the two $C_{cr's}$ obtained for each patient on different days in 505 patients.

Methods and Patients

Serum and urine creatinine concentrations were determined by autoanalyser method N-11B (Technicon Instruments Corp., Tarrytown, N.Y.). $C_{cr's}$ were based on 24-hour urine collections from patients mainly on medical wards. Bloods were drawn in the fasting state for determination of S_{cr}.

The records of 534 consecutive patients who had two or more 24-hour $C_{cr's}$ determined at the Queen Mary Veterans' Hospital were reviewed. 96% were male. When more than two $C_{cr,s}$ had been determined, the last two values were selected. 29 patients were rejected because they were not in steady state (values for S_{cr} differed by more than 20%) and the remaining 505 patients formed group I. Group II was formed of 236 group I patients selected because clearances were similar and appeared to closely approximate true values. Patients in group I were rejected in the formation of group II, if the difference between values for 24-hour creatinine excretion differed by more than 20% (n = 173), if 24-hour creatinine excretion was < 10 mg/kg (n = 31) and if records were inadequate (n = 65). $C_{cr's}$ in group II patients ranged from normal to as low as 11 ml/min (mean 72.7 $\pm$ SD 36.6 ml/min).

24-hour urine creatinine excretion was determined in duplicate in 249 males, including the 226 males in group II and 23 others who had been excluded from group II because the 24-hour creatinine excretion was < 10 mg/kg, but accepted here when 24-hour urine volume was > 500 ml.

$C_{cr's}$ were predicted in group II patients from values for S_{cr} using three published formulae and the formula derived in this study (table I). The mean of the two values for S_{cr}, if different, was utilized. Values for C_{cr} predicted by the three published formulae were calculated per 1.73 m^2 and adjusted according to each patient's surface area so as to be equivalent to the measured value. Two $C_{cr's}$ were also predicted for group II patients from a nomogram [4] using S_{cr}, age, sex and body weight, and the value calculated. The predictions were made without knowledge of measured $C_{cr's}$.

The values for C_{cr} predicted by each of the four formulae and the nomogram (table I) were compared with the mean of the two measured $C_{cr's}$ for each of the 236 group II patients. The means, correlation coefficients (r), regression lines ($y = a + bx$, where x is the measured and y is the predicted C_{cr}), standard errors of estimate and the deviations from the line identity,

$$\sqrt{\frac{\Sigma (x - y)^2}{n - 1}},$$

were calculated for each method of prediction. Similar correlations were made using logarithms of the predicted and the first measured $C_{cr's}$.

Table I. Formulae used to predict creatinine clearance from serum creatinine in males

	Formula	Reference
I	$\frac{100}{S_{cr}} - 12$ (ml/min/1.73 m²)	JELLIFFE [1]
II	$\frac{98 - 16\left(\frac{age - 20}{20}\right)}{S_{cr}}$ (ml/min/1.73 m²)	JELLIFFE [2]
III	$\frac{94.3}{S_{cr}} - 1.8$ (ml/min/1.73 m²)	EDWARDS and WHYTE [3]
IV	$\frac{(140 - age)\,(wt\ kg)}{72\,S_{cr}}$ (ml/min)	present study

Table II. Age, renal function and creatinine excretion in 249 patients

Age range years	Mean age years	n	Mean S_{cr} mg/100 ml	Mean C_{cr} ml/min	Mean Cr excretion mg/kg/24 h and SD
18–29	24.6	22	0.99	114.9	23.6 ± 5.0
30–39	34.6	21	1.08	98.6	20.4 ± 5.1
40–49	46.2	28	1.17	95.4	19.2 ± 5.8
50–59	54.4	66	1.49	77.9	16.9 ± 4.6
60–69	64.6	53	1.39	57.6	15.2 ± 4.0
70–79	74.4	42	1.78	38.6	12.6 ± 3.5
80–92	85.1	17	1.39	37.4	12.1 ± 4.1

Results

The mean 24-h creatinine excretion/kg body weight (CrUV24/kg) for each decade in males (table II) was plotted against the mean age in each decade (fig. 1) and the regression line determined from the mean values:

$$\text{CrUV24/kg (mg/kg)} = 28 - (0.2 \times \text{age in years}) \quad (1)$$

$$\text{CrUV24 (mg)} = 28 - (0.2 \times \text{age})\,(\text{wt kg}) \quad (2)$$

$$C_{cr}\,24\,(\text{ml/min}) = \frac{\text{CrUV24} \times 100}{1440\,S_{cr}} = \frac{(28 - 0.2\,\text{age})(\text{wt kg})}{14.4\,S_{cr}} = \frac{(140 - \text{age})(\text{wt kg})}{72\,S_{cr}\,\text{mg/100 ml}} \quad (3)$$

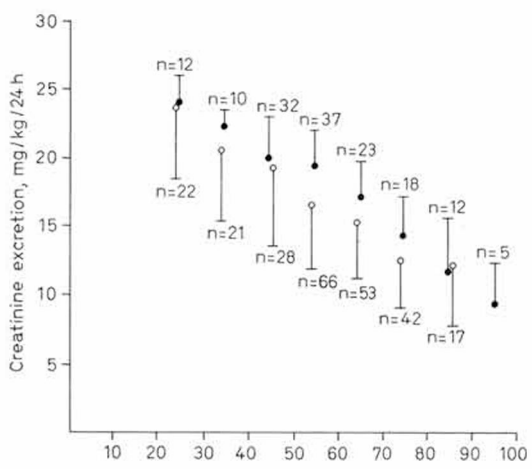

Fig. 1. Creatinine excretion. ● = SIERSBÆK-NIELSEN *et al.* [5], 149 males, age 20–99 years; ○ = present study, 249 males, age 18–92 years.

The average weight, in the numerator, approximates 72 kg for males, a figure which by chance is also in the denominator. Thus, for an average sized male:

$$C_{cr}\ \text{ml/min} = \frac{140 - \text{age}}{S_{cr}}$$

Comparison of measured values for C_{cr} with those predicted by the four formulae (table I) and the nomogram for the 236 group II patients, showed the formula derived in this study (formula IV) and the nomogram of SIERSBÆK-NIELSEN ranked in the first two, considering five parameters: The difference between measured and predicted means and the deviations from the line of identity (x = y) (table III); the correlation coefficients between measured and predicted values, and the slopes and intercepts of the regression lines (table IV). Formula II gave the least standard error of estimate (table IV), but the mean predicted C_{cr} underestimated the mean measured value by 9 ml/min. Formula IV and the nomogram gave remarkably similar results and the correlation coefficient between values for C_{cr} predicted by these two methods was 0.99.

The absolute value of the prediction error varies directly with the magnitude of the creatinine clearance (fig. 2), as does the difference between two measured creatinine clearances (fig. 3a). The use of log transformations as in

Table III. Mean group II predicted creatinine clearances (C_{cr}) and deviations of predicted values from the line of identity, determined by five methods (n = 236)

Method of predicting C_{cr}	Mean predicted C_{cr} ml/min[1]	Deviations from line of identity[2] (x = y)
Formula I	77.6	25.9
Formula II	63.6	24.0
Formula III	82.7	27.0
Formula IV	72.8	20.9
Nomogram	75.8	20.8

[1] Mean group II measured C_{cr} was 72.7 ml/min.

[2] $\sqrt{\frac{\Sigma(x-y)^2}{n-1}}$.

Table IV. Correlations between mean measured and predicted creatinine clearances in group II (n = 236)

Mean measured C_{cr} correlated with C_{cr} predicted by	r	SEE	Intercept[1]	Slope[1]
Formula I	0.73	21.7	31.0	0.64
Formula II	0.80	17.6	17.6	0.63
Formula III	0.74	20.6	38.2	0.61
Formula IV	0.83	19.8	14.0	0.81
Nomogram	0.84	19.5	15.4	0.83

[1] $y = a + bx$ where x and y are the measured and predicted creatinine clearances; a is the intercept and be the slope.

figure 3c, appears to result in comparable absolute differences at all levels of C_{cr}. Correlation coefficients and standard errors of estimates of log transforms also showed formula IV and the nomogram to give the best and equal results.

The prediction error expressed as a percentage of the C_{cr} appears relatively constant at all levels of C_{cr}. Analysis of individual results obtained using formula IV showed that predicted and mean measured values differed by 35% or less in 95% and by 20% or less in 67% of patients.

The correlation coefficients between the two measured C_{cr}'s in group I and II patients were 0.77 (SEE 25.5) and 0.94 (SEE 12.8), respectively. This

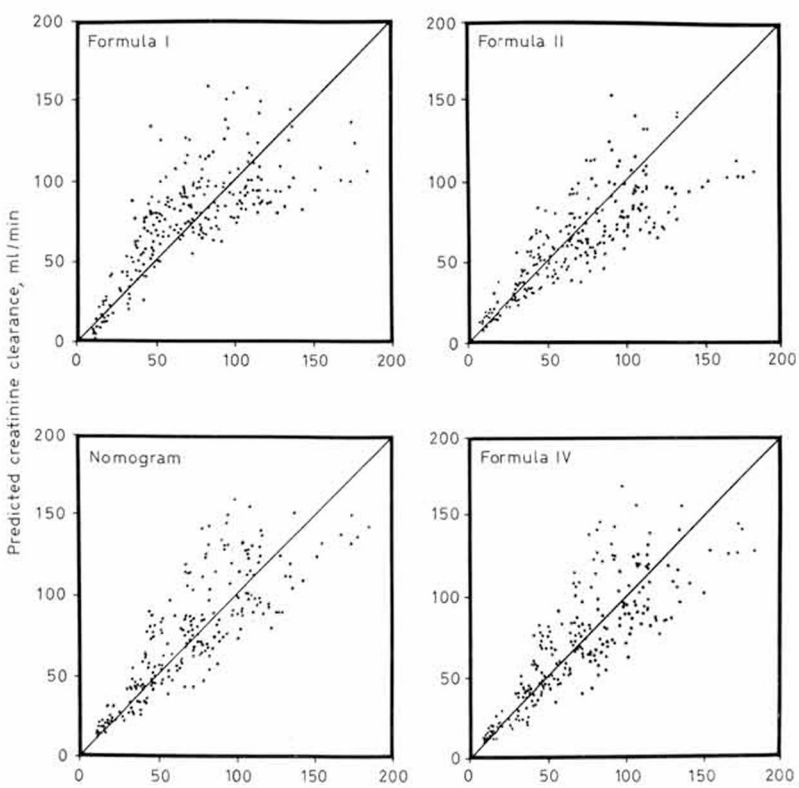

Fig. 2. Predicted and measured creatinine clearance.

compares with r values of 0.83 and 0.84 between measured and predicted C_{cr}'s for group II patients for formula IV and the nomogram (table IV). When log transforms were considered, the correlation coefficient was 0.83 between the two C_{cr}'s in group I patients and 0.90 between measured and predicted values for both the nomogram and formula IV in group II patients.

Discussion

A fall in glomerular filtration rate with age was described by DAVIES and SHOCK [6] in 1950 and has subsequently been confirmed, in particular for C_{cr} [7]. The decline in creatinine excretion with age is, however, less well

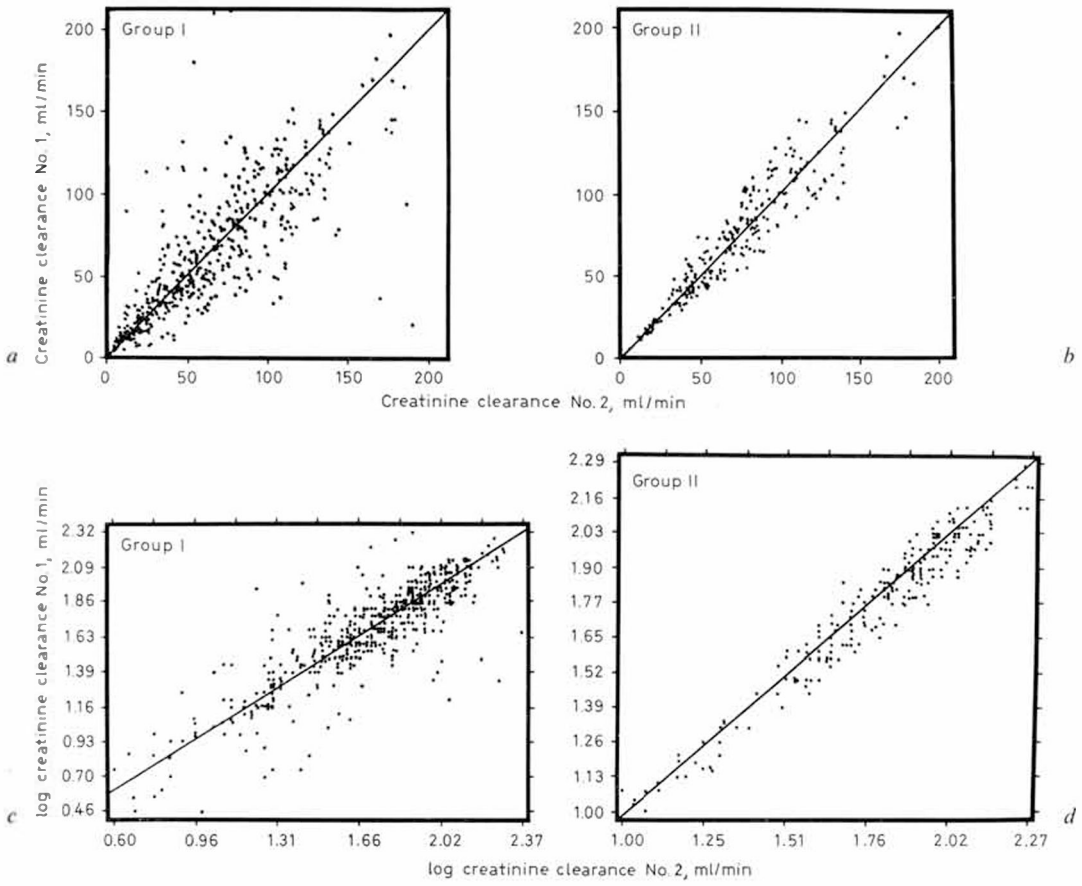

Fig. 3. Creatinine clearance (a, b) and log creatinine clearance (c, d) for groups I (a, c) and II (b, d).

recognized. We have demonstrated an almost linear decrease of about 50% (23.6 to 12.1 mg/kg) in creatinine excretion expressed in mg/kg/24 h over the 3rd to 9th decades, results which are remarkably similar to those of SIERSBÆK-NIELSEN *et al.* [5] (fig. 1) and AHLERT *et al.* [8]. Although the reason for this decline is not completely understood, it is probably related to a decrease in muscle mass with aging. Apart from varying the relationship between S_{cr} and C_{cr}, it has practical importance when creatinine excretion is used to evaluate the completeness of urine collections, and especially when S_{cr} is used to estimate the dose of toxic drugs excreted primarily by the kidneys. For

instance, a man of 70 might have the same S_{cr} as a 25-year-old man, but only half the C_{cr}.

Formulae I and III do not take age into consideration and give less satisfactory results (tables III, IV), with mean clearances predicted for group II patients exceeding the measured means by 7 and 10 ml/min, respectively. Overestimation would be expected to increase with age.

Formulae II includes age as a factor, but was found to underestimate the measured C_{cr} by an average of 9 ml/min. Results using this formula are said to compare well [3] with those obtained using a computer program [9] which is basically derived from the data of KAMPMANN *et al.* [4]; however, a factor based on experience in a limited number of patients is included, which reduces predicted values for C_{cr} by 15%. Our data, measured in hospitalised males, are strikingly similar to those of SIERSBÆK-NIELSEN *et al.* [5] (fig. 1), suggesting this 15% reduction is unnecessary.

The values predicted by formula IV and the nomogram of SIERSBÆK-NIELSEN *et al.* [5] gave the best predicted results. Both methods gave means which closely approximated the mean measured value for group II patients and very similar correlation coefficients and regression lines considering predicted and measured values (table IV). The correlation coefficient between C_{cr}'s predicted by these two methods was 0.99. We recognize that the same group II patients were used in the derivation of formula IV as in the test group and therefore the results of predictions in another group might not be as good.

The correlation coefficients found in group II patients between mean measured C_{cr}'s and those predicted by formula IV and the nomogram were 0.83 and 0.84, compared with values found between paired creatinine clearances performed in the same selected 236 group II patients of 0.94 and of 0.77 in the 505 group I patients who were randomly selected. These results indicate that on average, prediction error will not exceed the difference between two creatinine clearances determined in the same individual on a hospital ward. The difference between two measured C_{cr}'s is due to biological variation and to errors related to urine collection and creatinine assay; it is not possible to quantitate their relative contributions in this study. However, we suggest that urine collection errors were the largest source of variation. It should also be noted that group II patients are included in group I and that results obtained, if two entirely different groups were compared, might be somewhat different.

We have not evaluated the method of JADRNY [10] or the nomogram of EFFERSOE [11] for predicting C_{cr}; neither includes a factor for age.

Prediction of C_{cr} from S_{cr} has several limitations. These include demonstrated prediction error, the requirement for a steady state, factors related to age, sex and height, the need for a normal relationship between muscle mass and total body weight, and the limitations related to the use of creatinine to measure renal function.

It is difficult to calculate a meaningful confidence limit for prediction of C_{cr} using absolute figures and standard statistics, because the absolute error varies directly with the magnitude of the C_{cr} and our population was not normally distributed in terms of C_{cr}. The percentage error, however, remains constant in relationship to the magnitude of the C_{cr}. An analysis of individual cases indicates that using formula IV, 95% of predictions will give a C_{cr} within 35% of the measured value (fig. 2).

Formula IV is based on data from adult males, Because of different relative amounts of fat and muscle in women, a correction is required. Various authors [2–4] have recommended reducing the predicted C_{cr} by 10–20%. A 15% reduction appears appropriate. We have no experience with children.

The omission of height, which is only a minor variable compared with weight in nomograms, which predict body surface area in adults, permits determination of the C_{cr} from age, weight and S_{cr}, without relating the value to body surface area of 1.73 m^2. This simplification would appear to lead to little loss of accuracy in adults [12].

Prediction of C_{cr} will not be accurate unless renal function and S_{cr} are at steady state, any more than will C_{cr} be accurate when determined using a S_{cr} after a sudden major change in renal function. C_{cr} can be greatly overestimated from S_{cr} in the early phase of acute renal failure before the S_{cr} has risen appreciably. When the change in renal function is less extensive and sudden, and one knows the rate of change, the S_{cr} can be estimated for a given period to give a rough value for clearance.

Certain patients had predictably low creatinine excretion for age and body weight on the basis of lower than usual muscle mass. The lowest value, 5.8 mg/kg/24 h, was found in a 59-year-old male with myotonic dystrophy; 24-hour urine volume was 2,000 ml, creatinine excretion 250 mg, C_{cr} 24 ml/min and S_{cr} was 0.7 mg/100 ml. These values were representative of several collections obtained with the aid of a bladder retention catheter. Thus, the S_{cr} may be falsely low and give an artificially high predicted C_{cr} when muscle wasting has occurred. Creatinine excretion was as much as 40% below predicted in a number of paraplegics who had urine collected with the aid of bladder retention catheter; the low values were presumably due to muscle

atrophy. Patients with marked obesity or ascites also excreted less creatinine per kilogram than expected. Although we have not corrected for excess fat or fluid because of inadequate data, a correction to lean or ideal body weight is advised when these abnormalities are pronounced.

Evaluation of renal function using S_{cr} and C_{cr} has certain limitations. C_{cr} may exceed inulin clearance by 50 to over 100% [13] because of secretion, particularly with declining renal function and with heavy proteinuria [13, 14]. C_{cr} predicted from the S_{cr} would also exceed inulin clearance in both these circumstances. There may be a diurnal variation in serum creatinine of up to 30% with the peak around 19.00 h; this is believed due to dietary intake [15, 16]. Thus blood should be drawn in the fasting state for S_{cr} determinations. 24-hour creatinine excretion and C_{cr} may vary from day to day, frequently by 10–20% [17].

S_{cr} can vary by 10% or more depending on the method used; higher values are given by methods which measure non-creatinine chromogens [15, 18]. Predicted C_{cr} would be reduced artificially by this amount. Similarly, as creatinine values determined on whole blood exceed those on serum [15], clearances predicted using blood creatinine would be artificially low. The method used in this study has been found to give values close to those found by methods which measure non-creatinine chromogens for serum creatinine [15, 18]; the upper limit of the normal range has been found to be 1.4 mg/100 ml in males and 1.2 mg/100 ml in females [15].

Some evidence suggests that as serum creatinine rises, creatinine production declines [11], possibly because of feedback inhibition, increased bacterial creatinine breakdown in the intestine [19], or decreased consumption of food and loss of muscle mass. There is little to suggest that this would be an important variable in determining serum creatinine concentration, except perhaps when renal function has been reduced to about 15% of normal [11, 20].

This study suggests that in spite of definite limitations, prediction of C_{cr} and S_{cr} is accurate enough to be useful under many clinical circumstances, provided age and body weight are considered in the calculation. Errors related to prediction appeared not to exceed variation due to errors associated with urine collection and creatinine assay, and to biological variation under ordinary hospital conditions in the adult.

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