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Creatinine clearance estimation from serum creatinine values: evaluation and comparison of five prediction formulae in Nigerian patients

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Summary
Predicability of creatinine clearance (CrCl) from serum creatinine would reduce the cost of renal care and obviate the need for 24-hours urine collection. Correlations have been established between serum creatinine (Scr) and 24-hour urinary creatinine clearance with derivation of various formulae. We have tested the applicability of these formulae in 34 Nigerian patients (22 males, 12 females) aged 18 to 58 years, (mean age 34.97± 11.20 years) with established chronic renal failure (CRF) mean Scr level 742.26±388.15 mol/L. 32 age and sex matched healthly adults with serum creatinine values below 120 umol/l., served as controls. Serum creatinine and 24 hour CrCl levels were determined on two consecutive occasions. Creatinine clearance values were also derived from Scr using each of the established prediction formulae: Cockcrof and Gault [1] Gates [2] Hull *et al* [3]; Jelliffe [4]; and Mawer *et al* [5]. A relationship was sought between measured CrCl and the predicted values (derived) using the stated formulae. Regression equation were generated and correlation coefficient r, coefficient of determination r^2, F- ration, prediction error, all defining the nature and strength of relationship were determined. We observed that good and statistically significant correlations exist between measured CrCl values and those predicated from the formulae (r ranging from 0.908 to 0.968 and r20.82 to 0.93 $P = 0.000$) and that a linear relationsip exists in all cases. Cockcroft and Gault formula gave the highest coefficient of determination r2 = 0.94. It is concluded that the existing formulae are adequate for determining CrCl from Scr and should be frequently used in the long term follow-up of patients with Chronic Renal Failure (CRF) in our setting.

Keywords: *Chronic renal failure, measured creatinine clearance, predicted creatinine clearance*

Résumé
La predictivite de la disparation de la creatinene (Crcl) du serum pourpai reduire le lout des soins renaux et rendre moins necesaire le beroin de recupere les wines pendant 24 heures. Des cor relations ont ete etablies entre le taux de creatinine du serum et celui obtenu dans les urines pendant 24 heures avec la derivation de pluneurs formules. Nous avons teste l'applica b'lite de les formules chez 34 patients Nigerians (22 homues, 12 femmes) ages de 18 a 58 ans (moyene d'age 34.97 I1 1,20 ans) ayant une insufisance renale chronique etablit (CRF). Leur taux moyenne de coeatinine de seruue scr etait de 742, 26 ± 388, 15 mol/L. T rente-deux adults en bonne sante de meme asfe et de meme sexe avec un taux de creatinine en dessous de 120 umol/l., avaient servis comme controle. Les taux de creatinine du seruu et les 24 heures deCrcL avient ete determine a 2 occasions consectives. Lesvaleurs dedisparition de la creatinine aveaient aussi ete dervices dee serumeen utilesant chancene des formular prea establis de predication. Cockcraft et Gault [10]; Gates [2], Hull *et al* [3], Jelliffe [4]; et mainer *et al* [5]. Une relation avait ete chercher entre le taux mesure de Crcl et les valuer predicitives (derives) en utilisant les for mules mentoine plus trout. Les equations de regression etaient gener's et les efficients de correlations, coefficients de determine tions r^2, le ration-f, l'erreur de predication, toute definissant la nature et la force de la realtion avaient et determine,. Nous avons observe quit yavait une bonne correlation et statisti quement significative existant entre lestaux merures de Crcl et colles predite par les formules. (r = entre 0, 908 et 0.968 et r^2 = 0.82 a o, 93 $P = 0.00$) et quil y avait ume relation lineaure dans tous les las.) La formule de cockroft et Gault avait donne le plus fort coefficent de determination $r^2 = 0.94$. Il a donc ete conduct que les formules existantes tont adequate pour determine la Crcl a partir du Crcl et cesformules devraient etre constaineut utilise's dans le suire des patients ayant des insuffisance renales chronique dans notre eviro nement.

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Introduction

Glomerular Filtration Rate (GFR) is defined as volume of blood or plasma cleared of a substance per unit time [6]. It is an important index of clinical course of the renal disease, thus its determination has become a routine investigation in clinical practice.

Accurate determination of GRF in clinical practice is beset with a number of problems These problems relate to the difficulty in performing the measurement which sometimes leads to imprecise estimate of GFR. Accurate assessment of GFR required measurement of renal clearance utilizing an ideal filtration marker such as; Inulin 99m Tc diethlene thiamine pentaacetic acid (99m Tc DTPA) ^{125} I iothalamate ^{51} Cr ethylene diamine tetra-acetic and (^{51}Cr-EDTA) [7].

The procedure for the use these filtration markers is cumbersome and time consuming and sometimes exposes the patients to irradiation [7]. Although there are a lot of setbacks on the use of endogenous creatinine clearance as an index of renal function, it still remains the best tool available in clinical practice. The procedure for determining endogenous creatinine clearance is the traditional timed 24-hours urine collection to estimate the creatinine excreted, urine volume, and plasma creatinine concentration, and these variables are mathematically related [8]. However, this procedure itself is inconvenient and expensive [9]. Also the accuracy of the result is affected by the method of urine collection and /or patients compliance, diet [8], exercise [8], drugs [10,11], muscle drugs [10,11], muscle mass [12], tubular secretion [7], and extra renal creatinine elimination (i.e., in faeces and sweat) [7].

For rapid and reliable determination of creatinine, clearance the result of which would be comparable to measured Crcl several formulae have been established. [1-5]. These formulae have been applied by various workers in the determination of GFR. However, some results are inconsistent with the expected GFR thus leading to sharp criticisms of the use of these formulae. There is the need to review these formulae to determine their utility and usefulness in Nigerian patients. In Nigeria, CFR is prevalent (prevalence ranges between 1.6% - 8%), renal centers are few and patients have a travel long distances to get to these centers. [13]. There is a progressive increase in the cost of management of these patients. Since 24 hours urine collection is unreliable if unsupervised, the use of serum creatinine as a determinant of creatinine clearance will unsupervised, the use of serum creatinine as a determinant of creatinine clearance will obviate the need for collection of 24-hour urine. It will also reduce the overall cost of the management of the patients. It is in view of these that this study was carried out.

Patients and methods

This study was carried out on 32 healthy subjects and 34 patients in established chronic renal failure with serum creatinine levels consistently above 177 umol/l. Only patients passing at least 500 ml of urine in 24 hours and who had not been previously dialysed were recruited into the study. None of the patients or normal subjects were on any of the following drug: saliclate, co-trimoxazole, trimethoprim, cimetidine or probenecid. Patients with massive oedema, jaundice, liver disease, and ketosis were excluded. The causes of chronic renal failure were chronic glomerulonephritis in 24 patients); hypretensive nephrosclerosis in 7, diabetic nephropathy in 1, sickle cell nephropathy in 1, and amyloidosis in 1.

All patients were admitted into the Renal Ward of the hospital for a period of 48-72 hours. After a through explanation of the procedure, a supervised 24 - hour urine collection was commenced between 7.00 a.m and 7.00 a.m of the following day with all the urine emptied into a 4 litre plastic container containing 15 ml of hydrochloric acid as preservative. At the end of urine collection, and in fasting state, 10 ml of venous blood was taken into lithium heparin specimen bottles for chemical analysis. Urine volume was also determined and an aliquot taken for electrolytes, creatinine and protein estimation. The patients were weighed with light clothing using the portable way master weighing scale (with a sensitivity of 50 gm). Also their ages which were approximated to their nearest birthday were recorded.

The normal subjects consisted of doctors, nurses, medical students and laboratory technologists. They went through similar procedures as above. Blood and urine creatinine estimations were done using diacetylmonoxime and Kinetic Jaffe method [14].

Statistical methods

The statistical package used to analyse the data was SPSS for Windows - Release 5.0.1 (October 1992) by SPSS Incorporation of USA on PC 386 DX. The mean, standard deviations, correlation and linear regression analysis, were done. The prediction error was determined by the use of paired mean difference at 95% CI between the measured and predicted CrCl and student t-test for paired samples was used for statistical significance. The linear relationship between the measured and predicted CrCl was evaluated using the formula.

$$tc = \frac{r\sqrt{n-2}}{1-r^2} \text{ at 95\% CI } = \sqrt{\text{F-ratio}}$$

where r = correlation coefficient;
r^2= coefficient of determination;
c = confidence interval;
F-ratio = prediction error.

Also the comparison of the derived formulae under consideration was done to decide which is the best in predicting Crcl. The criteria used were (i) the closer the r-value (correlation coefficient) to 1 the better the equation (ii) the higher the r^2 value the better the equation, (iii) the closer the slope value to 1 the better the equation, (iv) the closer the intercept value to zero the better the equation, (v) the lower the prediction error at 95% CI the better the equation, (vi) the higher the F-ratio the better the equation.

Results

The means age for the patients was 34.9 ± 11.2 years (age range 18-58 years), while the mean age for male and female patients were 33.8 ± 10.5 years and 37.0±12.5 years ,respectively.

The mean age for the patients was 58.8 ± 10.2 kg and the mean weight for male and female patients were 62.2±9.9 kg and 52.5±7.8 kg, respectively. The mean serum creatinine for male and female patients were 682.0±354.5 mmol/l and 866.7±433.5 umol/l (266-1719umol/L), respectively, (P = 0.189). The mean urinary creatinine excretion for male patients was 7636.0 ± 3889. lumol/24 hours and for female patients it was 7329.6 ± 4084.9 umol/24 hours (*P* = 0.83; Table 1). The mean serum creatinine and SD for the controls was 85.3 ± 33.2 umol/l.

Table 1: Comparison of parameters in patients by sexes

			X	SD	P-value
Age (Yr)	Total	n = 34	34.97	11.20	
	Male	n = 32	33.86	10.53	
	Female	n = 12	37.00	12.57	
					0.444
Weight (Kg)	Total	n = 34	58.80	10.24	
	Male	n = 22	62.20	9.99	
	Female	n = 12	52.58	7.86	
					0.0007
Serum Creatinine (umol/l)	Total	n = 34	797.26	386.15	
	Male	n = 22	682.09	354.56	
	Female	n = 12	866.75	433.50	
					0.189
Urinary Creatinine (umol/24hrs)	Total	n = 34	7527.94	3899.94	
	Male	n = 22	7636.09	3889.18	
	Female	n = 17	7329.67	4084.90	
					0.831

Correlation between measured and predicted CrCl

Table 2: Regression parameters between measured and predicated creatinine clearance in patients and controls.

Patients	CC(r)	CD(r^2)	Slope	Intercept
Jelliffe	0.91	0.83	1.00	-1.4
Mawer *et al*	0.96	0.93	0.93	1.2
Cockcroft & Gault	0.97	0.94	0.96	-0.7
Hull *et al*	0.97	0.94	0.91	1.3
Gates	0.93	0.87	1.11	0.1
Controls				
Jelliffe	0.72	0.52	0.77	22.1
Mawer *et al.*	0.96	0.92	0.88	11.4
Cockcroft & Gault	0.96	0.91	0.91	11.2
Hull *et al*	0.96	0.92	0.87	12.1
Gates	0.81	0.65	0.67	27.0

CC = Correlation coefficient
CD = Coefficient of determination

Table 2 shows the regression and parameters between the measured and predicted creatinine clearance in patients and controls. In this study all the five formulae gave a good correlation in both health and disease states.

Fig.1: Measured vs Predicted creat. clearance in controls

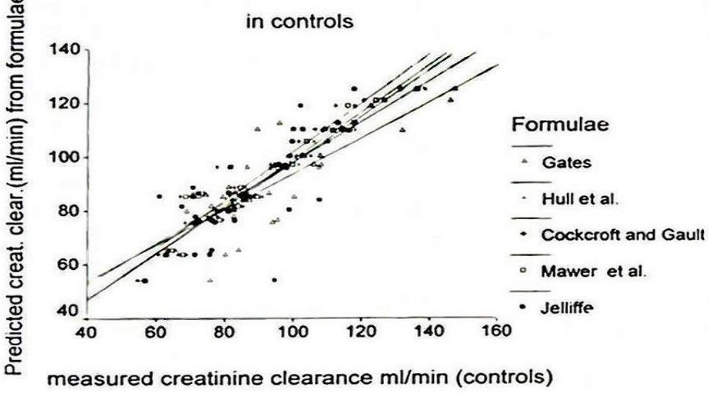

Fig. 2: Measured Creat. clearance vs Predicted Creat. Clearance in Patients

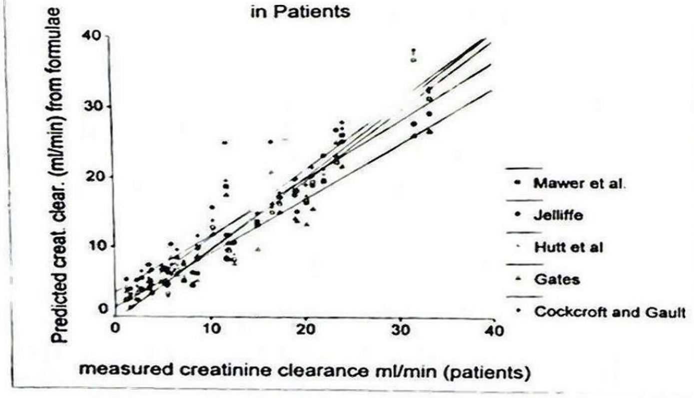

Figure 1 shows a correlation graph between the measured CrCl and each of the five formulae in patients while figure 2 shows a similar correlation graph in controls. The values for tc obtained in patients for measured and predicted CrCl, respectively for Jelliffe, Mawer *et al*, Cockcroft and Gault, Hull *et al.*, and Gates formulae were 12.31, 20. 70, 21.66, 21.46 and 14.55. Similarly, in controls, tc values for Jelliffe, Mawer et al., Cockcroft and Gault, Hull et al., and Gates formulae were 5.65, 18.09, 17.86, 18.10 and 7.44 respectively, indating a significant linear relationship in each case.

Influence of sex on predictability

Table 3: Regression parameters between measured and predicted creatinine clearance by sex in patients and controls

Patients		CC (r)	CD (r^2)	Slope	Intercept
Jelliffe	M	0.94	0.89	1.05	-1.05
	F	0.77	0.59	0.58	1.11
Mawer *et al.*	M	0.98	0.95	0.93	1.76
	F	0.86	0.74	0.73	1.76
Cockcroft & Gault	M	0.98	0.95	0.97	-060
	F	0.87	0.76	0.76	0.46
Hull *et al.*	M	0.98	0.95	0.92	1.56
	F	0.86	0.73	0.72	2.00
Gates	M	0.95	0.90	1.11	0.83
	F	0.77	0.59	0.79	1.27
Controls					
Jeliffe	M	0.87	0.75	0.81	21.75
	F	0.58	0.33	0.87	3.45
Mawe *et al.*	M	0.96	0.91	0.85	14.74
	F	0.96	0.92	0.93	6.45
Cockcroft & Gault	M	0.95	0.91	0.88	14.00
	F	0.95	0.91	0.98	5.55
Hull *et al.*	M	0.96	0.91	0.84	15.03
	F	0.96	0.91	0.93	6.45
Gate	M	0.88	0.77	0.70	22.37
	F	0.78	0.61	1.41	-26.77

M = Male *CC = Correlation Coefficient*
F = Female *CD = Coefficient of Determination*

Table 3 shows the influence of sex on predictability of CrCl with the use the five prediction formulae. There was good correlation in respect of gender in the diseased state. However, female genders have lower values of correlation -[7] and coefficient determination (r^2). While r and (r^2) values vary from 0.94 to 0.98 and 0.89 to 0.95, respectively, in males, they are 0.77 to 0.87 and 0.59 to 0.76 in females.

Comparison of the formulae in patients and controls:

Table 4: Comparison of formulae to determine which is best in disease state

Norma:	JL	MW	CG	HL	GT
r	0.908	0.965	0.968	0.967	0.932
r^2	0.826	0.931	0.936	0.935	0.869
Slope	1.006	0.938	0.957	0.913	1.110
Intercept	-1.368	1.202	-0.730	1.268	0.140
f.ratio	151.469	428.597	469.105	460.501	211.734
P.E + SD	+3.600	+2.338	+2.211	+.337	+3.225
95%CI	0.029-	-1.309	- 0.534	-1. 063	-2.444-
	2.542	0.322	2.077	0.568	-0.193

Table 5: Comparison of formulae to determine which is best I health

Normal Subjects	JL	NW	CG	HL	GI
r	0.718	0.957	0.956	0.957	0.805
r2	0.156	0.916	0.914	0.916	0.648
Slope	0.765	0.884	0.914	0.865	0.673
Intercept	22.080	11.419	11.209	12.135	26.991
F-ration	31.962	327.360	318.104	327.482	55.293
P.E.	-1.164	-1.083	-3.810	-0.011	3.768
+SD	+12.945	+5.600	+5.438	+5.777	+12.607
95%CI	-5.832-	-3.103-	-5.772-	-2.0772-	-0.779-
	3.504	0.936	-1.850	2.094	8.314

JL = *Jelliffe;*
HL = *Hull et al.*
GT = *Gates*
MW = *Mawer et al*
CG = *Cockcroft and Gault;*
P.E. = *Predication Error*
SD = *Standard Deviation*
95% CI = *Confidence Interval*

Tables 4 and 5 show the values obtained when the formulae under consideration were compared using the parameters r, r^2, F-ratio, slope intercepts in both patients and controls respectively.

Discussion

GFR is an important index of measurment of clinical course of renal disease, and also a useful tool in the management of such patients. There is the need to find ways of having a reproducible and reliable GFR as many times as the physicans need it without significiantly increasing the cost of management and/or imposing some difficulties to the patients. This study examined the relative utility and accuracy of predictive formulae for CrCl not only in Nigerian patients as had been done before [9,15] but also in healthy volunteers. The five formulae gave high (good) correlation and accuracy in both patients and to a lesser extent in healthy controls. This is in contrast to the finding of Robertshaw *et la* who observed that in healthy subjects with normal renal function, the correlation coefficients were not very high while the predication error was rather high [16]. All the five formulae also gave a good correlation when separated into male and female gender. However, the correlation parameters in females have lower values compared to males thus, the equations are still usefull in both sexes.

The Cockcroft and Gault formla provided the most saitisfactory assessment of creatine clearance (CrCl) as an index of renal function in this study out of all the five formulae under consideration. The superior quality of cockcroft and Gault formula is reflected by the high values of r,r^2, a slope closed to unity, a low intercept, a high F-ratio, and the relative ease with which the formula is remembered. However, its prediction error was found to be higher than others in both patients and controls. The superior quality of Cockcroft and Gault formula in this study is in agreement with earlier work in Nigeria [9] and other populations [17,18]. compared with this Taylor *et al* [15] evaluated four formulae and found that there was a significant difference between the measured and predicted CrCl. Walster *et al* [19] suggested that the poor estimate of GFR by cockcroft and Gault formula in advanced renal failure might to due to the fact that the formula was dervied from hospitalised persons of whom the majority had normal renal function. in this study, neither sex nor extreme of serum creatinine concentration appeared to have an important effect on correlation between the predicted and measured CrCl as judged from regression parameters and prediction error. The formulae appeared to be of equal predictive value irrespective of the level of serum creatinine concentration in the patients and in healthy controls.Thus using predictive formulae and particularly that of Cockcroft and Gault formula endogenous Crcl can be reliably and validy predicted in both healthy individuals and in chronic renal disease patients.

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