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Utility of Cystatin-C in hospitalized patients. Comparison with different methods of assessing renal function

F. J. Cepeda*, E. Fernández*, A. Pobes and L. M. Baños****
*Clinical Laboratory Department. **Nephrology Department. Hospital of Cabueñes (SESPA). Gijón.

SUMMARY

Serum creatinine is the most widely used parameter to assessing renal function, even though limitations, some time is necessary meassure 24 h creatinine clearance (CLcr), or estimate Cockroft-Gault (C-G) or MDRD formulas. Different methods can offer different results, and cause confusion in clinicians. Using Cystatin-C as new parameter of renal function could suppose an important improvement. The objective of our study was to compare the different methods from renal evaluation and establish the utility of cistatina-C in the hospital area. In the study were included 70 patients (44 men) selected of random way, predominate patients with kidney disease and diabetics, which was made CLcr and calculated C-G and MDRD formulas. The mean age of the patients was 66 ± 14years, mean weight 73 ± 17Kg, creatinine 2,14 ± 1,77 mg/dL, cystatin-c 1,77 ± 1,18 mg/L, CLcr 54,39 ± 36,2 mL/min. The correlation of 1/Crea with the Clcr, C-G and MDRD formulas was respectively: 0,7735, 0.8269 and 0.9613, (p < 0.0001). The correlation of 1/Cist with the Clcr, C-G and MDRD was respectively: 0,836, 0.8142 and 0.832, (p < 0,0001). By Bland-Altman graphs the average of the difference between CLcr with CG and MDRD was 2,8 mL/min and -1,5 mL/min respectively. Comparing CG with MDRD was 1,7 mL/min. The average of the observed absolute differences between CLcr with CG and MDRD was 13.5 mL/min and 17.1 mL/min respectively. Between this formulas the average was 12.5 mL/min. Statistically significant differences between the different methods from renal evaluation do not exist (p > 0,05). In conclusion, most of the urine collections could be avoided with the use of the formulas. Cystatin-c is far beyond the creatinine, mainly to detect slight renal alteration (sensitivity 80,4% US 44,7% in men) becoming a promising alternative, that could reduce considerably hidden renal insufficiency (non detected by creatinine), although more studies are needed to confirm.

Key words: ***Glomerular filtration rate (GFR). Creatinine clearance. Cystatin-C. Cockroft-Gault formula. MDRD formula.***

Correspondence: Fco. Javier Cepeda Piorno
Hospital de Cabueñes
Cabueñes, s/n
33222 Gijón (Asturias)
E-mail: j_cepeda_p@hotmail.com

UTILIDAD DE LA CISTATINA C EN EL ÁMBITO HOSPITALARIO. COMPARACIÓN CON LOS DISTINTOS MÉTODOS DE VALORACIÓN RENAL

RESUMEN

La prueba utilizada habitualmente para valorar la función renal es la creatinina sérica, aunque por sus limitaciones, en muchas ocasiones es necesario recurrir a la medida del aclaramiento de creatinina en orina de 24 horas (Clcr), la fórmula de Cockroft-Gault (CG) o la fórmula de Levey (MDRD). Los distintos métodos pueden dar distintos resultados, creando una situación de confusión a los clínicos. La introducción de la Cistatina-C como nuevo marcador de función renal, podría suponer una mejora considerable. El objetivo de nuestro estudio fue comparar los distintos métodos de valoración renal y establecer la utilidad de la cistatina-C en el ámbito hospitalario. Fueron incluidos en el estudio 70 pacientes (44 hombres) seleccionados de manera aleatoria, predominando enfermos renales y pacientes diabéticos, a los que se les realizó el CLcr y se calculó CG y MDRD. La edad media de los pacientes fue 66 ± 14años, peso medio 73 ± 17Kg, creatinina 2,14 ± 1,77 mg/dL, cistatina-c 1,77 ± 1,18 mg/L, CLcr 54,39 ± 36,2 mL/min. La correlación entre 1/Crea con el Clcr, CG y MDRD fue respectivamente: 0,7735, 0,8269 y 0,9613, (p < 0,0001). La correlación entre 1/Cist con el Clcr, CG y MDRD fue respectivamente: 0,836, 0,8142 y 0,832, (p < 0,0001). Mediante los gráficos de Bland-Altman la diferencia media observada entre CLcr con C-G y MDRD fue -1,5 mL/min y 2,8 mL/min respectivamente. Comparando CG con MDRD fue 1,7 mL/min. La media de las diferencias absolutas observadas entre CLcr y CG fue 13,5 mL/min y con MDRD fue 17,1 mL/min. Entre ambas fórmulas la media fue 12,5 mL/min. No existen diferencias estadísticamente significativas entre los distintos métodos de valoración renal (p > 0,05). En conclusión, la mayoría de las recogidas de orina podrían evitarse con la utilización de las fórmulas. La Cistatina es muy superior a la creatinina, sobre todo para detectar leve alteración renal (sensibilidad 80,4% vs 44,7% en hombres) convirtiéndose en una alternativa prometedora que reduciría a más de la mitad la IRC oculta generada por la creatinina, aunque se necesitan más estudios para confirmarlo.

Palabras clave: ***Tasa de filtración glomerular. Aclaramiento de creatinina. Cistatina-C. Fórmula de Cockroft-Gault. Fórmula MDRD.***

INTRODUCTION

Renal function assessment in hospitalized patients is paramount both from a prognostic point of view and for assessing and adjusting the different therapeutic regimens in elderly and poly-medicated patients.

The best method to assess renal function is measuring the glomerular filtration rate (GFR)[1], although accurate estimation by means of administrating exogenous agents (inuline, iodine-thalamate, DTPA, iohexol) is difficult in daily clinical practice and is seldom performed since these are expensive and technically complex tests that cannot be repeatedly done.[2, 3]

As an alternative, creatinine clearance (CrCl) measurement by 24-hour urine collection is used. Even at the hospital setting, its measurement may be inaccurate,[4] so that several formulas have been developed to estimate CrCl, among which the Cockcroft-Gault formula (CG in mL/min)[5, 6], derived from the study of 249 patients without renal disease, is the most accepted one. Multiple calculations have also been developed to estimate GFR from serum creatinine (sCr) and a series of patient's individual variables by means of multiple regression analysis.[7,8,9] The accuracy of such calculations is adequate provided that they are applied to groups of patients with characteristics similar to those of patients included for designing the mathematic formula. Thus, several authors have designed specific formulas for groups with identical pathologies, such as paraplegic, obese and cancer patients, as well as those with severe infections and trauma.[10,11 12,13,14]

In spite of the advantages the formulas provide, there are special situations in which the use of these equations is not recommended[15] and collection of 24-hour urine will be necessary (Table 1).

Because of these limitations and the lack of accuracy of these formulas, research has focused on the search for new agents that may replace serum creatinine. The most promising one seems to be Cystatin-C (Cyst) that, besides getting very close to the ideal marker of GFR as many recently notifications endorse,[16] is showing to be a new independent risk factor for cardiovascular morbimortality.[17]

The aim of our study was comparing the different methods used to assess renal function at the hospital setting and establishing the utility of cystatin-C.

MATERIAL AND METHODS

This a cross-sectional descriptive study for a 1-month period, at a 500-bed hospital. Seventy adult patients (44 males and 26 females) were randomly included, to whom their family practitioner ordered CrCl to assess their renal function. Patients and the nursing staff received the usual instructions to collect the urine.

The same day, the ordering physician or the nursing staff registered the patient's weight (registered only in 50 patients) together with the remaining demographical data needed for the equations. Height was only gathered in a small number of patients so that correction by body surface area was not possible. Mean age for the patients was 66 ± 14 years (range 23-92), mean weight 73 ± 17 Kg (range 41-130), creatinine 1.2 mg/dL (median, 95% CI: 1.1-1.6; range 0,7-7,7), cystatin-C 1.77 ± 1.18 mg/L, CrCl 54.39 ± 36.2 mL/min (see Table 2).

Patients origin was as follows: internal medicine (45); nephrology (9), urology (4), gastroenterology (4), cardiology (3), respiratory medicine (2), other (3). In the study group there were 34 renal patients (48%), 18 diabetics (26%), and 18 patients with multiple pathologies. Twenty patients had increased CRP (29%).

The samples were processed the same day that extraction was done to determine creatinine (Jaffé's kinetic method, Advia, Bayer, 4.8% CV control). To determine cystatin-C, the samples were frozen according to the manufacturer's specifications (immunonephelometric method, Dade Behring, 5 % CV control).

The formulas used for the calculation of CrCl, CG formula, and abbreviated MDRD (MDRD-4) are indicated in Table 3.

The correlation between serum parameters (1/sCr, 1/Cyst) determined by the different assessment methods was calculated by Pearson's r.

The level of disagreement between the different methods was studied by the Bland-Altman graphs from the value of the differences obtained with the different measurements. The level of statistical significance was set at $p < 0.05$.

The accuracy of the different methods was calculated by the mean of the absolute differences observed and the 25th, 75th, and 90th percentiles of the absolute differences between methods.

Table I. Conditions in which the use of equations ti measure renal function is not recomended

- Acute renal failure
- Hyponutrition
- Muscle pathology
- Severe liver disease
- Limb amputations
- Special diets: vegetarian, creatin-rich
- Drugs blocking creatinine secretion (cimetidine, trimethroprim)

Table II. Characteristics of the study group

	Mean	Median	Deviation standard
CREATININE (mg/dL)	2.14	1.25	1.77
CYSTATIN-C (mg/L)	1.77	1.26	1.18
CrCl (mL/min)	54.39	53.05	36.2
C-G (mL/min)	54.44	58.13	31.75
MDRD (mL/min/1.73 m^2)	51.6	55	28.63
WEIGHT (kg)	73	74	17.18
AGE (years)	66	68.5	14.11

Table III. Methods used to assess GFR that were compared in our study

- CREATININE CLEARANCE IN 24-HOUR URINE (mL/ min).

CL crea = [sCr (urina) (mg/dL) x V (mL)]/crea(serum)(mg/dL)

- GAULT-GAULT FORMULA (mL/min).

CG = [(140 – AGE (years) x WEIGHT (kg)] x (0.85 in women) / (72 x sCr (serum)(mg/dL).

- ABBREVIATED MDRD FORMULA OR LEVEY'S MODIFIED FORMULA (mL/min/1.73 m^2).

MDRD = 186 x sCr (mg/dL)$^{-1,154}$ x AGE (years)$^{-0,203}$ x 0.742 (in women) x 1.212 in black race.

To establish whether there were differences between measurement methods, the t test was used. All statistical analyses were done with the Med Calc software for Windows.

RESULTS

The correlation between 1/CrCl and CrCl, CG and MDRD was, respectively: 0.7735 (95% CI: 0.658-0.853; p < 0.0001), 0.8269 (95% CI: 0.711-0.899; p < 0.0001) and 0.9613 (95% CI: 0.938-0.976; p < 0.0001).

The correlation between 1/Cyst and CrCl, CG and MDRD was, respectively: 0.836 (95% CI: 0.748-0.895; p < 0.0001), 0.8142 (95% CI: 0.691-0.891; p < 0.0001) and 0.832 (95% CI: 0.742-0.893; p < 0.001). The correlation between creatinine and cystatin values was 0.936 (see Figure 1).

The mean difference (MD) observed between measured CrCl and calculated CrCl by the CG and MDRD formulas was, respectively: -1.5 mL/min (95% CI: -38.3 to 35.3), and 2.8 mL/min (95% CI: -41.5 to 47.1). When comparing the CG formula with MDRD, the mean difference was 1.7 mL/min (95% CI: -33.5 a 36.9). The results are shown in Figure 2.

The mean of the absolute differences observed between CrCl and CG and MDRD formulas were, respectively: 13.5 mL/min (95% CI: 9.7-17.2) and 17.1 mL/min (95% CI: 13.6-20.6); between both formulas, the mean was 12.5 mL/min (95% CI: 8.7-16.1). Table 4 shows the absolute differences between the different measurement methods, at 25th, 75th, and 90th percentiles.

There are no statistically significant differences between CrCl and CG (P = 0.5782), between CrCl and MDRD (P = 0.3046), or between CG and MDRD (P = 0.5079).

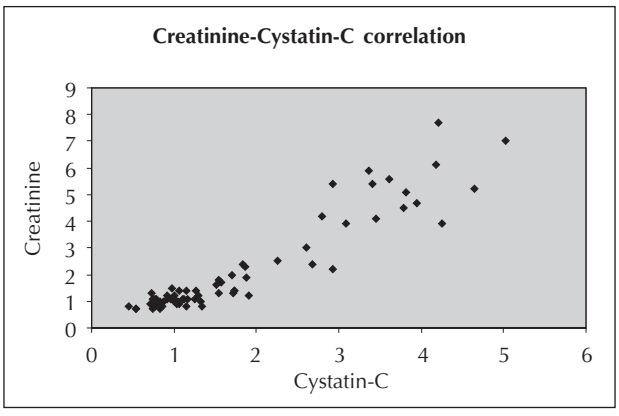

Fig. 1.—Correlation between Creatinine and Cystatin-C values (r = 0.9357).

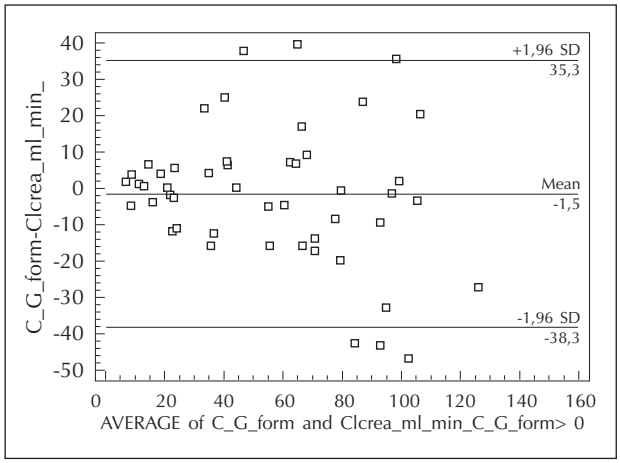

Fig. 2.—Bland-Altman graphs comparing CrCl and CG.

Taking CrCl as the reference, decreased GF levels (< 90 mL/min) would be detected by means of creatinine, with sensibility (S) = 44.7% and 55.6% (in males and females, respectively). Specificity (Sp) = 100%. Cystatin-C had S = 80.4%, Sp = 57.1%. To detect a higher level of impairment (< 60 mL/min), creatinine showed S = 64% and 71.4%, Sp = 95% and 100% (in males and females, respectively). Cystatin-C showed S = 97.4%, Sp = 58.1%.

By using MDRD, to detect decreases of 90 mL/min/1.73m^2, creatinine showed sensibilities of 39.5% and 45.5% (in males and females, respectively), Sp = 100%. Cystatin-C, S = 76.9%, Sp = 80%. To detect decreases of 60 mL/min/1.73m^2, creatinine showed S = 68% and 66.7% (in males and females, respectively), Sp = 100%. Cystatin-C, S = 92.5%, Sp = 53.3%. In this way, we may identify 40 patients with CRF (GFR < 60 mL/min/1.73m^2). Among them, 8 patients had normal creatinine values, which represent a 20% rate of occult renal failure (5 women and 3 men, in spite of a higher proportion of male patients in the study group). By using cystatin-C we would

Table IV. Absolute differences between the different methods used at 25th, 75th and 90th percentiles

Compared Methods	Mean (mL/min) ± SD	Percentile (95% CI) 25th	75th	90th
CL crea-CG	13.47 ± 13.02	3.93 (1.57-6.73);	19.87 (12.05-33.39);	37.12 (20.95-44.36)
CrCl-MDRD	17.14 ± 14.84	4.30 (2.56-9.36);	26.30 (18.54-30.47);	37.00 (29.00-46.25)
CG-MDRD	12.45 ± 12.90	3.03 (1.95-7.62);	17.19 (10.48-24.52);	28.28 (17.40-53.12)

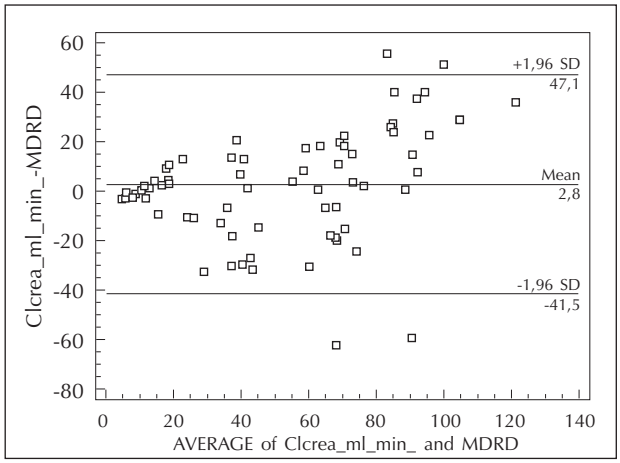

Fig. 3.—Bland-Altman graphs comparing CrCl and MDRD.

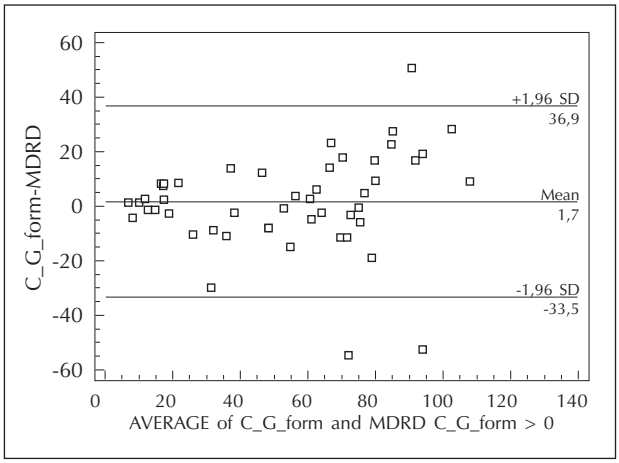

Fig. 4.—Bland-Altman graphs comparing CG and MDRD.

only have 3 patients with normal cystatin values and decreases in GFR (2 women and 1 man), so that occult CRF rate would be reduced to 7%.

DISCUSSION

The test usually performed to assess GFR is serum creatinine due to its readiness and simplicity. It is however widely known that it is far from being an ideal marker of GFR,

because it is highly influenced by GFR itself as well as other factors such as muscle mass, gender, age, diet, ethnicity, and tubular secretion.[18] This makes necessary to establish a large reference range so that it makes it poorly sensitive to mild GFR changes. In our study, this poor sensibility was shown, which was about 40%-50% to detect mild renal impairment.

The use of CrCl is not devoid of drawbacks. In the past, by using the classical Jaffé's method (alkaline picrate) to measure creatinine, very accurate values were obtained regarding GFR. Nowadays, with the improvement of detection methods, the interference with chromatogenous agents is reduced obtaining lower creatinine values, closer to the real ones. This apparent improvement makes that real GFR is overestimated when calculating CrCl. For this reason, the MDRD (Modification of Diet in Renal Disease) proposes to use a correction factor of 0.81 when CrCl needs to be used.[4] In our study, it is clearly observed how CrCl yields higher values than the CG formula (MD = 1.5 mL/min), and even higher than the MDRD formula (MD = 2.8 mL/min). We also observed a high inaccuracy in the results by comparing CG (mean of the absolute differences 13.5 mL/min) or MDRD (mean of the absolute differences 17.11 mL/min). However, by comparing the formulas between each other, this inaccuracy slightly decreases (mean of absolute differences 12.5 mL/min). A large number of studies show that the error in predicting GFR from equations is lower than the one that occurs by measuring CrCl, not only due to errors in urine sample collection but also in daily variations in GFR and creatinine secretion.[19, 20, 21]

For theses reasons, creatinine and CrCl are not good methods to assess renal failure progression.[22]

Rolin *et al.*[23] investigated on a group of patients with wide ranges of GF. They verified that the CG formula was poorly faithful and especially inaccurate (9.8 ± 34.2 mL/min; CV 48.1%). The authors concluded that the formula would justified in those cases with urgent need. Further studies with different groups showed better results, with variation coefficients between 13% and 22%.[24]

Levey *et al.*[20] reported that the equation 7 derived from the MDRD study (that included 1070 patients) was more accurate for estimating GF than CrCl measured or estimated by CG. The equation has been validated in patients with severe end-stage CRF and in renal transplanted patients, but it did not included patients with normal renal function. Another study compared this formula with a simpler one from the MDRD study, which only included four variables (MDRD-4) but that presented an accuracy and bias similar to more complex equations of the MDRD study, so that it was concluded that this could be the recommended equation to generally estimating GFR.[4,25]

In addition to the inaccuracy, formulas are subject to measurement errors produced by intra-essay and intra-individual creatinine variability, the lack of

standardization in calibrations between different laboratories, and to measurement errors of the remaining variables in the equations.[26] This may explain the contradictions shown between the different studies. The recently proposed standardization of creatinine calibrations by the Laboratory Working Group of the National Kidney Disease Education Program (NKDEP) may represent a notable advance, although until the end of the year 2008 we will not be able to compare the results.[27]

With all this in mind, it has to be considered that estimation is only an rough calculation and not an exact measurement. To appropriately use the formulas, the clinician has to be aware of their limitations.

In our study, we verified the high inaccuracy of the different used methods to assess renal function, especially within ranges close to normality, and this accuracy improves when GF decreases, we assume that this is due to the higher accuracy of the measurement with higher creatinine values.

Recently, the Spanish Society of Nephrology, the National Kidney Foundation «K/DOQI Clinical Practice Guideline for Chronic Kidney Disease», and the European guidelines have recommended to clinical laboratories to report GF estimations, either by using the CG formula of the MDRD for adults, together with the creatinine value.[4,28]

In view of our results, and once the high inaccuracy of estimations has been checked, we find it useful to report as «normal GF» (> 90 mL/min) or «slightly decreased GF» (60-90 mL/min) and only in those cases with GFR < 60 mL/min to report the value obtained. Thus, the clinician will have a more real and accurate information and the results sent by the laboratory would be felt as being more reliable. The National Kidney Disease Education Program (NKDEP) of the National Institutes of Health (NIH) and K/DOQI guidelines provide with similar recommendations to make a more rational use of equations estimating the GFR.

Once the limitations of creatinine and the related equations have been shown, cystatin-C

emerges as a promising tool for managing the renal-vascular pathology.

The meta-analysis carried out by Dharnidharka *et al*.[28] proves this by using correlation coefficients and ROC curves (area under the curve).

In our study, one striking result is that 1/Cyst shows better correlation with measured CrCl than with 1/sCr and as good correlation as with CG and MDRD formulas, in spite of being an independent parameter that is not implicated in these formulas, by contrast with creatinine. This indicates its adequate correlation with GF. It is also shown how cystatin-C is very superior to creatinine regarding the detection of mild renal impairment, with a sensibility almost twice as high and allowing dramatically reducing the rate of occult CRF obtained with creatinine. Patients benefiting from this test would specially be those with low muscle mass, such as the elderly and women, which represent large groups of hospitalized population. Since it is an exact method and not an estimation, contrary to equations, it could be a highly valuable tool for the follow-up and even to assess the prognosis of patients with renal failure.

The drawbacks that it may have would be its intra-individual variability,[29] and its change in certain pathologies such as thyroid disease,[30] as well as the high cost as compared with creatinine. Some authors have also found that cystatin values may be influenced by the use of corticosteroids or may be related with age, gender, weight, height, cigarette smoking, or high CRP levels[31], so that large studies are needed in order to confirm the interferences that this technique may have.

The limitations of our study likely are the small number of patients and the lack of a gold standard, so that we can only establish mere comparisons and sense which could be the best method to assess GFR based on what has been published and in the coherence of our results. The fact of having included a higher number of male patients may have biased the sensibility results between genders, although this is not a fact specially concerning, just to approximately know the differences between creatinine and cystatin-C. The lack of the height for all patients has prevented us from correcting the results by body surface area, which could represent a limitation for comparing between the different methods assessing renal function. However, in seldom occasions these data are available in daily practice to carry out corrections, as it is in our case, so that we verified that there are no differences between the different methods. This is likely due to the fact of working with patients with decreased renal function, which is precisely the case where the different methods show the highest level of agreement and thus correcting by body surface area may have the least impact. Otherwise, we may consider that the goals of this study have been achieved.

To conclude, measurement of CrCl may be replaced, in most cases, by the use of equations, which would allow obtaining more readily and accurate results in patients' follow-up and saving considerable amounts of material and health care efforts. In our case, due to the characteristics of the studied hospital population (with a predominance of elderly patients with renal disease) we consider that the MDRD formula is more adequate. As Omar *et al*.[32], we believe that cystatin-C may become an appropriate marker for identifying mild renal disease in large groups of

people and to assess their progression, specially in those situations in which formulas are poorly accurate and their use is not recommended. Further studies will be needed to confirm whether this technique may replace serum creatinine.

REFERENCES

1. Rose, BD. Chapter 3: Renal Circulation and Glomerular Filtration Rate: Clinical Physiology of Acid-base and Electrolyte disorders. New York, NY, Mc-Graw Hill, 1984.
2. Haim N, Oman SD, Galai N, Burde B, Nathan S, Catane R: Estimation of creatinina clearance without 24 hour urine collection. A useful Guide during Cisplatin therapy. *Acta Oncol* 32: 409-412, 1993.
3. Star y cols.: New markers for Kidney Disease (Editorial). Clin Chem 48 (9): 1375-1376, 2002.
4. National Kidney Foundation K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. *Am J Kidney Dis* 39 (S1-200), 2002.
5. Cockcroft DW, Gault MH: Prediction of creatinina Clearance from serum creatinine. *Nephron* (16): 31-41, 1976.
6. Robertshaw H, Lai Kn, Swaminathan R: Prediction of creatinina clearance from plasma creatinina: comparison of five formulae. *Br Clin Pharmacol* 28: 275-280, 1989.
7. Walser M, Drew HH, Guldan Jl: Prediction of glomerular filtration rate from serum creatinina concentration in advanced chronic renal failure. *Kidney Int* 44: 1145-1148, 1993.
8. Nankivell BJ, Gruenewald SM, Allen RD, Chapman JR: predicting glomerular filtration rate after kidney transplantation. *Transplantation* 59: 1683-1689, 1995.
9. Baracskay D, Jarjoura D, Cugino A, Blend D, Rutecki GW, Whittier FC: Geriatric renal function: estimating glomerular filtration in an ambulatory elderly population. *Clin Nephrol* 47: 222-228, 1997.
10. Mirahmandi Mk, Byrne C, Barton C, Penera N, Gordon S, Vaziri ND: Prediction of creatinina clearance from serum creatinina in spinal cord injuri patients. *Paraplegia* 21: 23-29, 1983.
11. Salazar DE, Corcoran GB: Predicting creatinina clearance and renal drug clearance in obese patients from estimated fat-free body mass. *Am J Med* 84: 1053-160, 1988.
12. Robinson BA, Frampton CM, Colls BM, Atkinson Ch, Fitzharris BM: Comparison of methods of assessment of renal function in patients with cancer treated with Cisplatin, Carboplatin or Methotrexate. *Aust NZ J Med* 20: 657-662, 1990.
13. Cronberg S, Nordstrom L, Ringberg H: Prediction of creatinina clearance by several methods in patients with severe infections. *Eur J Clin Pharmacol* 42: 193-195, 1992.
14. Davis GA, Chandler MH: Comparison of creatinina clearance estimation methods in patients with trauma. *Am J Hosp Pharm* 53: 1028-1032, 1996.
15. Rodrigo Calabria E: Medida de la función renal. Evaluación del cociente microalbuminuria/creatinina. Valor de la tira reactiva y del examen del sedimento urinario. Indicaciones para solicitar ecografía renal. *Nefrología* 24: S6, 2004.
16. Arias IMª, Pobes A, Baños M: Cistatina C. Nuevo marcador de función renal. *Nefrología* (Editorial) 25 (3): 217-220, 2005.
17. Shlipak MG, Sarnak MJ, Katz R, Fried LF, Scliger SL, Newman AB, Siscovicks DS, Stehman-Breen C: Cystatin C and the risk of Death and Cardiovascular events among elderly persons. *N Engl J Med* 352: 2049-2060, May 19, 2005.
18. Perrone RD, Madias NE, Levey AS: Serum creatinina as an index of renal function: new insights into old concepts. *Clin Chem* 38: 1933-1953, 1992.
19. Walser M: Assesing renal function from creatinina measurements in adults with chronic renal failure. *Am J Kidney Dis* 32: 11-23, 1998.
20. Levey AS, Bosch JP, Greene T, Rogers N, Roth D: A more accurate method to estimate glumerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 130: 461-470, 1999.
21. Lewis J, Agodoa L, Cheek D, Greene T, Middleton J, O'Connor D y cols.: Comparison of cross-sectional renal function measurements in African Americans with hypertensive nephrosclerosis and of primary formulas to estimate glomerular filtration rate. *Am J Kidney Dis* 38: 744-753, 2001.
22. Walser M, Drew HH, La Funce ND: creatinina measurements often yield false estimates of progression in chronic renal failure. *Kidney Int* 34: 412-418, 1988.
23. Rolin HA, May PM, Wei R: Inaccuracy of estimated creatinina clearance for prediction of iothalamate glomerular filtration rate. *Am J Kidney Dis* 4: 48-54, 1984.
24. Frits AW Kemperman, Raymond T Krediet, Lambertus Arisz (Editorial Review). Formula-derived prediction of the glomerular filtration rate from plasma creatinina concentration. *Nephron* 91: 547-558, 2002.
25. Boston AG, Kronemberg F, Ritz E: predictive performance of renal function equations for patients with chronic kidney disease and normal serum creatinina levels. *J Am Soc Nephrol* 13: 2140-2144, 2002.
26. European Best Practice Guidelines for Haemodialysis (part 1). Measurement of renal function. *Nephrol Dial Transplant* 17 (Supl. 7): 7-9, 2002.
27. Gary L Myers, W. Grez Millar, Josef Coresh, James Fleming, y cols.: Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. *Clinical Chemistry* 52 (1): 5-18, 2006.
28. Dharnidharka VR, Kwon C, Stevens G: Serum Cystatin-C is superior to serum creatinina as a marker of kidney function: a meta-analysis. *Am J Kidney Dis* 40 (2): 221-6, 2002.
29. Keevil BG, Kilpatrick ES, Nichols SP, Maylor PW: Biological variation of Cystatin C: implications for the assessment of glomerular filtration rate. *Clin Chem* 44: 1535-9, 1998.
30. Deinum J, Derkx FHM: Cystatin for estimation of glomerular filtration rate? *Lancet* 356: 1624-5, 2000.
31. Omar F Laterza, Christopher P Price, Mitchell G Scott: (Review) Cystatin C: An improved estimator of glomerular filtration rate? *Clin Chem* 48 (5): 699-707, 2002.
32. Lesley A. Stevens, Josef Coresh, Tom Greene, Andrew S: Levey. Assessing Kidney Function. Measured and Estimated Glomerular Filtration Rate. *N Engl J Med* 354: 2473-83, 2006.