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Cut-off value of proteinuria/creatininuria ratio predictor of proteinuria = 150 mg/24h in a sample of Argentinean students. Its utility in proteinuria categorization

Valor de corte del cociente proteinuria/creatininuria predictor de proteinuria = 150 mg/24 h en una muestra de estudiantes argentinos. Utilidad de su aplicación para categorización de la proteinuria

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Abstract

Introduction: Proteinuria is a kidney damage marker. KDIGO 2012 categorizes 24h proteinuria (PER), mg/24h, or proteinuria/creatininuria ratio in isolated sample (PCR), mg/g, in: A1, normal-slightly increased: <150; A2, moderately increased: 150-500; A3, severely increased: > 500. PER is the gold standard, PCR was incorporated to avoid 24h collection but the numerical equivalence between both is controversial. The maximum normal value, 150 mg/24h, has diagnostic / prognostic relevance in Chronic Kidney Disease.

Objectives: to determine in a sample of students: a) correlation of PCR in first morning urine with PER, b) cut-off value (VdC) of PCR predictor of PER = 150 mg/24h, c) concordance between both methodologies for categorization A according to the PCR values of KDIGO 2012 and the VdC found.

Methodology: Descriptive, analytical, cross-sectional study. Sample: 51 students. Determinations in 24h urine and first morning. Proteins: Red Pyrogallol-Molybdate method; creatinine: Jaffé kinetic. Correlation: Spearman coefficient; Concordance: Bland-Altman and kappa. VdC: ROC analysis (receiver operating curve). Programs: Excel and Medcalc. 95% CI, p <0.05.

Results: Proteinuria (median/interquartile range), PER (mg/24h): 106.00/83.64-137.82; PCR (mg/g): 58.00/50.50-87.00; p = 0.025; Spearman coefficient: 0.5540; Bland-Altman mean of the differences (PER-PCR): 31.4. AUC = 0.883 (95% CI 0.762-0.956), VdC = 82 mg/g, S=90 %, E=82.9 %, RP + = 5.27, RP- = 0.12. Concordance in categorization A: kappa using PCR 150 mg/g: 0.106 (95% CI -0.134-0.347), poor-mild; kappa using V de C found: 0.4568 (95% CI 0.2063-0.6505), mild-considerable.

Conclusions: The concordance in categorization A improves using the VdC. It emphasizes the importance of not using as equivalent PCR =150 mg / g and PER = 150 mg/24h to differentiate normal from increased proteinuria but to establish in each laboratory the corresponding V de C.

Key words: proteinuria, classification, diagnosis, chronic kidney disease, clinical laboratory techniques, creatinine, urine.

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Resumen

Introducción: la proteinuria es marcador clásico de daño renal. La organización Kidney Disease: Improving Global Outcomes (KDIGO) categoriza en 2012 la proteinuria de 24 h (PER) como mg/24 h o la relación proteinuria/creatininuria en muestra aislada (PCR) como mg/g así: A1, normal-levemente aumentada (<150); A2, moderadamente aumentada (150-500), y A3, severamente aumentada (>500). La PER es el gold standard y la PCR fue incorporada para evitar recolección de 24 h, pero la equivalencia numérica entre ambas es controvertida. El valor 150 mg/24 h tiene relevancia diagnóstica/pronóstica en enfermedad renal crónica.

Objetivos: determinar, en una muestra de estudiantes argentinos, la correlación de PCR en primera orina matutina con PER, el valor de corte (VdC) de PCR predictor de PER=150 mg/24 h y la concordancia entre ambas metodologías para la categorización A según valores de PCR de la clasificación KDIGO 2012 y del VdC hallado.

Materiales y métodos: estudio descriptivo, analítico y transversal realizado en una muestra de 51 estudiantes. Determinaciones en orina de 24 h y en la primera matutina. Proteínas: método rojo de pirogalol molibdato; creatinina: Jaffé cinético. Correlación: coeficiente de Spearman; concordancia: Bland-Altman y kappa. VdC: análisis ROC (receiver operating curve). Programas: Excel yMedcalc. IC95 %, p<0,05.

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Resultados: proteinuria (mediana/rango intercuartil), PER (mg/24 h): 106,00/83,64-137,82; PCR (mg/g): 58,00/50,50-87,00; p=0,025; coeficiente Spearman: 0,5540; Bland-Altman media de las diferencias (PER-PCR): 31,4. ABC=0,883 (IC95%: 0,762-0,956); VdC=82 mg/g; S=90 %; E=82,9 %; RP+=5,27; RP-=0,12. Concordancia en categorización A: kappa empleando PCR 150 mg/g: 0,106 (IC95%: -0,134- 0,347), pobre-leve; kappa empleando VdC hallado: 0,4568 (IC95%: 0,2063-0,6505), leve-considerable.
Conclusiones: la concordancia en categorización A mejora al utilizar el VdC. Destaca la importancia de no usar como equivalentes PCR=150 mg/g y PER=150 mg/24 h para diferenciar proteinuria normal de aumentada, sino la necesidad de establecer en cada laboratorio los VdC correspondientes.
Palabras clave: proteinuria, clasificación, diagnóstico, enfermedad renal crónica, técnicas de laboratorio clínico, creatinina, orina.

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Introduction

Proteinuria is a classic sign of kidney disease and, together with urinary albumin excretion, is one of the markers of kidney damage that is most widely used both for the diagnosis and prognosis of chronic kidney disease (CKD). The diurnal variation of the protein excretion in patients with glomerular diseases makes that their concentration in an isolated sample has no clinical usefulness.[1-3] The gold standard for their quantification is the 24 h proteinuria or protein excretion rate (PER). However, the complexity for the patient in the collection of urine of 24 h and the possibility that the total volume corresponding to the period is not sent to the laboratory has led many organizations to recommend replacing it with the relation between the proteins and creatinine present in an isolated sample (protein creatinine ratio, PCR). While the glomerular filtration rate remains stable, creatinine excretion has little variation during the day.

The quantification of proteinuria as protein/creatinine ratio[4] corrects the effect of the urine dilution or concentration on the concentration of proteins. The most accepted physiological value of daily protein excretion is up to 150 mg/24 h and there are different criteria to establish increased proteinuria and clinically significant proteinuria according to different guidelines,[5-10] being frequently used with clinical significance values > 300 or 500 mg/24 h. The Kidney Disease: Improving Global Outcomes (KDIGO) organization, in 2012, defines CKD as the presence of alterations in the renal structure (damage) or function for at least 3 months and with health implications.

Proteinuria is one of the markers of kidney damage; when it is present with values > 150 mg/24 h, associated with normal to high glomerular filtration rate (GFR) (> 90 mL/min/1.73 m^2) or slightly decreased (60-89 mL/min/1.73 m^2) persistent for more than 3 months and health implications, it defines that the patient would have CKD. The KDIGO 2012 also classifies proteinuria into three categories used to evaluate the risk of progression or complications of the kidney disease, being the quantitative increase of the proteinuria a factor of increased risk. (Table 1)

As shown in Table 1, the numerical values of PER and PCR for the cuts between categories are the same. This is because the PCR values were determined from those of the PER assuming a daily creatininuria of 1 g/day. Using different analytical methods, different ranges of proteinuria and different ways of collecting the sample to determine the PCR, many researchers have reported coincidences and discrepancies in the PCR values that predict the cut-off points by category according to the PER, which is the gold standard.

The maximum normal value of proteinuria has diagnostic/prognostic relevance in CKD by limiting categories A1 and A2, which means that an individual with proteinuria >150 mg/24 h with GFR values > 60 mL/min /1.73 m^2 for more than 3 months fulfills, in principle, the criteria for defining CKD. This also means that an individual with CKD and proteinuria > 150 mg/24 h will have a different prognosis than the one who does not have proteinuria or albuminuria. Considering the relevance of this value according to the current clinical guidelines and the

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Table 1. Relationship between the categories of albuminuria and proteinuria.

Determination	Categories		
	A1 Normal or slightly increased	A2 Moderately increased	A3 Severely increased
AER (mg/24 h)	<30	30-300	>300
PER (mg/24 h)	<150	150-500	>500
ACR (mg/g)	<30	30-300	>300
PCR (mg/g)	<150	150-500	>500
Reactive strip	Negative or traces	Traces (+)	(+) or more

AER: albumin excretion rate; PER: protein excretion rate; ACR: albuminuria/creatininuria ratio; PCR: proteinuria/creatininuria ratio.
Source: elaboration based on Kidney Disease: Improving Global Outcomes.[10]

practicality of the use of PCR as a screening test, it was proposed to determine in a sample of students of the career of Biochemistry of the Universidad Nacional del Litoral (UNL) the correlation of PCR in the first morning urine with PER, the cut-off value (VdC) of PCR predictor of PER=150 mg/24 h and the concordance between both methodologies for the categorization A applying the value of the PCR of the table and the VdC found.

Materials and methods

Descriptive, analytical cross-sectional study in which a sample of 100 voluntary students of the career of Biochemistry of the UNL was studied, convenience sample, between May, 2014 and June, 2016. The students were ambulatory, not pregnant, amputated or affected by consumptive diseases or acute pathologies. The 24-hour proteinuria was determined in all subjects; and the concentration of proteins and creatinine in the first morning urine, belonging to the same collection of 24 h was also determined in 51 of them, consecutive. The sample of students in whom the two determinations were made was composed of 44 women and 7 men and the female predominance was related to the composition by gender of the career. The age range was from 19 to 35 years, with a mean of 24.5 years.

The urinary proteins were determined by the pyrogallol red-molybdate colorimetric method and the creatininuria by the Jaffé kinetic method. Both were carried out manually with reading in Metrolab 1600 Plus spectrophotometer (UV-Vis Metrolab S.A., Bernal, Argentina). The GFR was estimated by the CKD-EPI equation using for the determination of serum creatinine the Jaffé kinetic method, traceable to Isotope Dilution Mass Spectroscopy (IDMS), in the Cobas c111 autoanalyzer (Roche Diagnostics Ltd. Rotkreuz, Switzerland).

The protocol was approved by the Ethics Committee of the Faculty of Biochemistry and Biological Sciences of the UNL and included informed consent and a questionnaire on data of the clinical history of the students and their families and their life habits.

The evaluation by the Shapiro-Wilk test did not allow us to assume the compliance of the assumptions of normality, so nonparametric statistics was used. The Wilcoxon test for paired data was used to analyze if the differences between PCR and PER were significant at a 95% confidence level; the Spearman's coefficient was used to evaluate the correlation between the tests; the Bland-Altman analysis and the kappa coefficient were used to study the agreement, and the kappa coefficient according to Landis and Koch was assessed for the analysis of the assignment to categories A.[11]

The ROC (receiver operating curve) analysis was used to find the VdC, determining area under the curve (AUC), sensitivity (S), specificity (E) and likelihood ratios (LR). Likewise, the students were classified into category A according to the values or PER and PCR, the kappa index was calculated and then they were reclassified to differentiate between

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A1 and A2 the VdC of PCR predictor of PER of 150 mg/24 h. A confidence level of 95 % (95% CI), p <0.05 was used in all cases.

Results

The characteristics of the sample studied and the values of PER and PCR are shown in Table 2.

It was proven that the differences in the medians between PER and PCR were significantly different from zero in the total group (Wilcoxon test for paired data; p=0.0003). The ratio between the values of PER and PCR is shown in Figure 1.

The Spearman's correlation coefficient (rho) was 0.557 (95% CI: 0.333-0.722; p <0.0001) and the mean of the differences between PER and PCR was 31.4. The concordance for proteinuria in accordance with PER and PCR of the whole sample according to the Bland-Altman analysis is shown in Figure 2.

Table 2. Median and interquartile range of age, creatininemia, eGFR, PER and PCR of the analyzed sample (n=51).

Variable	Median (interquartile range)
Age (years)	25 (23-26)
Creatininemia (mg/dL)	0.77 (0.67-0.85)
eGFR (mL/min/1.73 m^2)	111 (99-122)
PER (mg/24 h)	106.0 (83.6-137.8)
PCR (mg/g)	58.0 (52.5-88.0)

Source: Own elaboration.

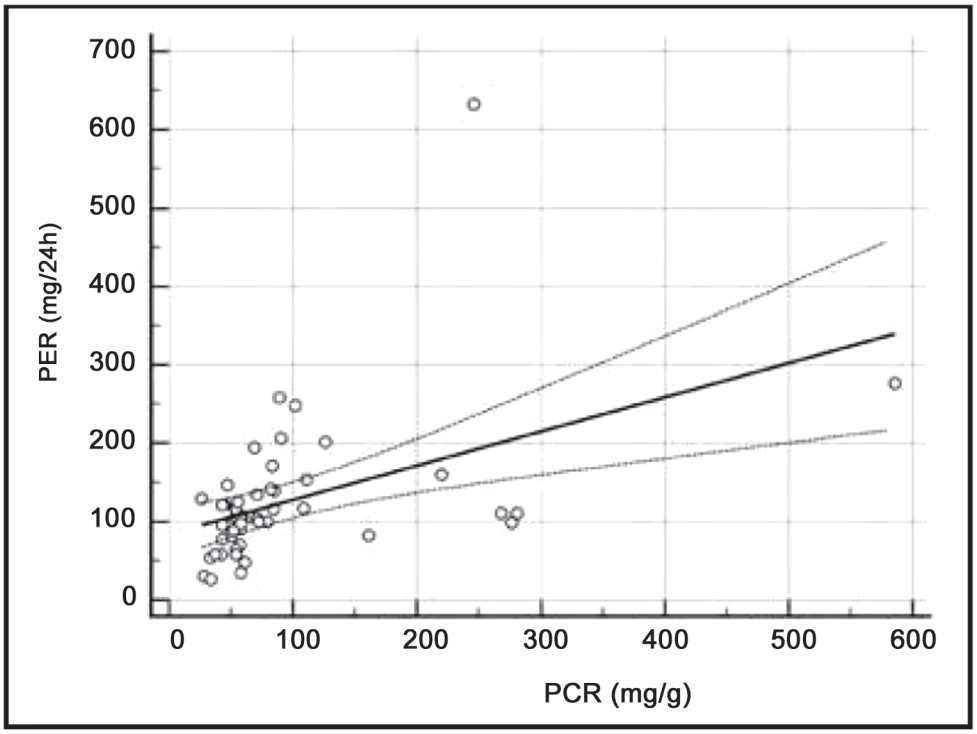

Figure 1. Relationship between the values of PER and PCR (n=51).
Source: Own elaboration.

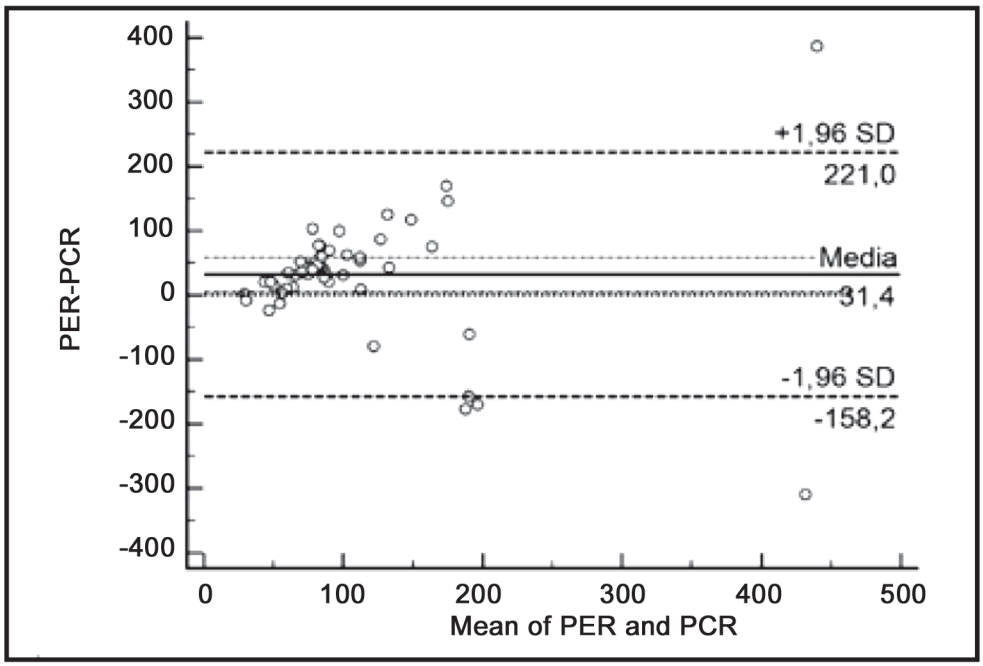

Figure 2. Bland-Altman plot for PER and PCR Note: the continuous center line represents the mean of the differences between the pairs of values of proteinuria by PER and PCR and the less spaced dashed lines represent the values corresponding to the upper and lower limits of the 95% CI for the mean of the differences. Source: own elaboration.

From the ROC analysis was obtained an AUC=0.883 with 95 % CI: 0.762-0.956 and p (Area=0.5) <0.0001. The ROC curve is shown in Figure 3.

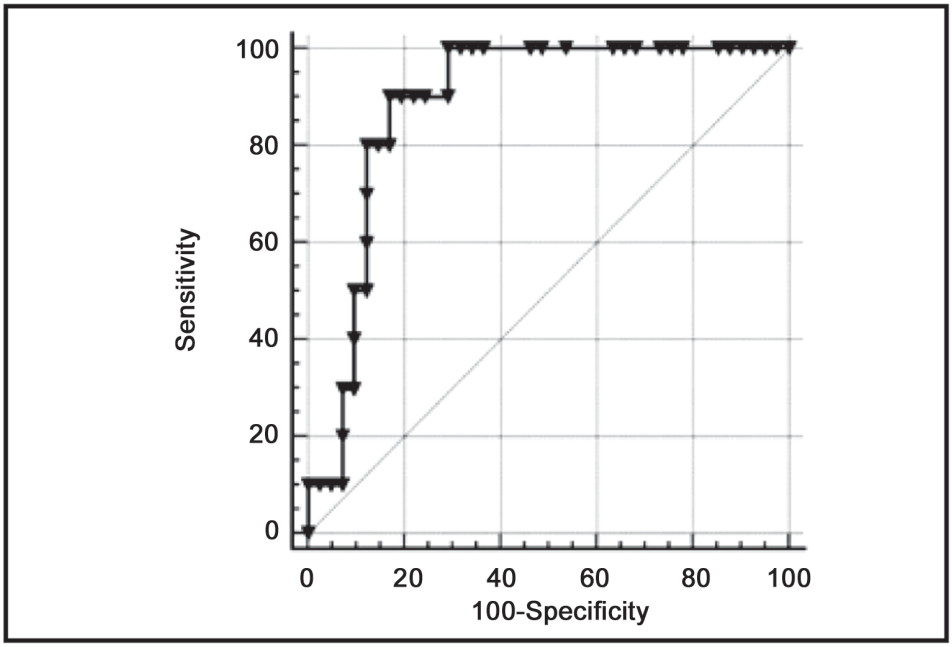

Figure 3. ROC curve of PCR in relation to the PER (n=51). Source: own elaboration.

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The VdC of PCR predictor of PER of 150 mg/24 h was obtained using the Youden's criterion. Table 3 shows the sensitivity, specificity and likelihood ratios for the VdC of 82 mg/g.

Both the LR+ and the LR- values were moderate.[12] The students were categorized according to PER and PCR using the cut-off values of Table 1 for both variables. The number of students included in each category is summarized in Table 4.

Table 4 shows that 38 students (74.5 %) were classified into the same category A by PER and PCR. Of the 51 students, 8 (15.7 %) passed to a category A of better prognosis when proteinuria was evaluated by PCR compared to the classified by PER and 5 (9.8 %) to a category of worse prognosis. The kappa index of agreement was 0.106 (95 % CI: -0.134-0.347), poor-slight according to the classification of Landis and Koch.

Using the cut-off value of 82 mg/g to differentiate the categories A1 and A2 by PCR, it was performed a new concordance analysis by kappa index, being its recalculated value of 0.505 (95 % CI: 0.269-0.741), acceptable-considerable according to Landis and Koch. Table 5 shows that 41 students (80.4 %) were classified into the same category A by PER and PCR.

Table 3. Sensitivity, specificity and likelihood ratios for the VdC of 82 mg/g obtained from the ROC analysis.

Cut-off value (mg/g)	Sensitivity	95% CI	Specificity	95% CI	LR+	LR-
82	90.00	55.5-99.7	82.93	67.9-92,8	5.27	0.12

Source: own elaboration.

Table 4. Concordance in the allocation to stage A according to proteinuria values by PER and PCR (n=51).

PCR	PER			
	A1 <150 mg/24 h	A2 150-500 mg/24 h	A3 >500 mg/24 h	n (%)
A1 (PCR<150 mg/g)	37	7	0	44 (86,3 %)
A2 (PCR 150-500 mg/g)	4	1	1	6 (11,8 %)
A3 (PCR>500 mg/g)	0	1	0	1 (2,0 %)
n (%)	41 (80,4 %)	9 (17,6 %)	1 (2,0 %)	51

Nota: Las celdas sombreadas indican los estudiantes clasificados en la misma categoría A según PER y PCR. Fuente: Elaboración propia.

Table 5. Concordance in the assignment to stage A according to the values of proteinuria by PER and PCR using as the limit for A1 for PCR the cut-off value of 82 mg/g (n=51).

PCR	PER			
	A1 <150mg/24h	A2 150-500mg/24h	A3 >500mg/24h	n (%)
A1 (<82 mg/g)	34	1	0	35 (68.6 %)
A2 (82-500 mg/g)	7	7	1	15 (29.4 %)
A3 (>500 mg/g)	0	1	0	1 (2.0 %)
n (%)	41 (80.4 %)	9 (17.6 %)	1 (2.0 %)	51

Note. The shaded cells indicate the students classified into the same category A according to PER and PCR. Source: own elaboration.

Discussion

The studies that link PCR and PER have found variable and mostly good correlations, as can be seen in the review of Price *et al.*,[13] which includes reports of works on 42 to 289 individuals. Anyway, the existence of correlation between the values does not indicate concordance and it cannot be assumed from a good coefficient that one method can replace another one.

Many of the studies have used different cut-off values of PCR to predict PER with adequate sensitivity and specificity, a large number of them to predict the value of 300 mg/24 h used in obstetrics for the diagnosis of preeclampsia:

Côté *et al.*,[14] in their review of 9 studies in hypertensive pregnant women, report cut-off values between 190 and 500 mg/g for a PER of 300 mg/24 h.

Morris *et al.*,[15] in their review of studies in patients with preeclampsia, find that the optimal cut-off points of PCR to detect proteinuria >0.3 g/24 h are between 300 and 350 mg/g, with sensitivity and specificity over 75 %, but they conclude that there is no enough evidence on how the PCR should be used in clinical practice due to the heterogeneity in the diagnostic accuracy and the prevalence of proteinuria among the different studies.

Gai *et al.*,[16] using pyrogallol red-molybdate to dose proteinuria and Jaffé kinetic for creatininuria, found a predictive value of 11.3 mg/mmol (100 mg/g) for a PER of 150 mg/24 h with 91% of sensitivity and 75 % of specificity in patients with nephropathies.

Guy *et al.*,[17] in 83 patients with kidney disease and using the same analytical methods than Gai *et al.*,[16] found in the ROC analysis that the PCR in the first morning urine showed to be a good predictor of PER > 150 mg/24 h (AUC=0.90; 95 % CI: 0.84–0.97) and better for PER> 300 mg/24 h. The optimal cut-off value of PCR predictor of PER > 150 mg/24 h was 23 mg/mmol (203 mg/g), sensitivity 78 %, specificity 79 %, LR+=3.7 and LR-=0.3.

Farías *et al.*,[18] in 120 patients with kidney disease and values of PER <3500 mg/24h, used sulfosalicylic acid to dose proteinuria, and Jaffé kinetic for urinary creatinine. In this way, they established that values of PCR > 76.8 mg/g in sporadic urine predicted high concentrations of PER with a sensitivity and specificity of 75.0 % and 90.0 %, respectively. These authors found that, for low values of proteinuria, in the Bland-Altman analysis, the points were arranged randomly around zero. In the sample of students processed at the UNL, the mean of the differences between PER and PCR was positive in these concentrations, underestimating PCR to PER in a mean value of 31.4.

Patil *et al.*,[19] also using sulfosalicylic acid and a modified Jaffé method, found in random urine a cut-off value of PCR predictor of PER > 150 mg/24 h of 0.1481 g/g (148.1 mg/g) for a S=96 %, E=98.9, LR+=102.76 and LR-=0.04.

Leman and Doumas,[20] using Coomassie brillant blue and alkaline picrate, obtained a good correlation (r=0.97) between the PCR in 24-hour urine and in spontaneous urine considering a whole range of normal to nephrotic urine. With this method they found the regression equation PCR (random sample) = 1.06 x PCR 24 h + 42 mg/g.

Leung *et al.*[21] studied the correlation in 82 patients with lupus using benzethonium chloride and Jaffé kinetic compensated correcting the excretion of proteins by body surface and they found a Spearman correlation coefficient of 0.91 for a normal to nephrotic range and cut-off points of 0.45; 0.70 and 1.84 mg/mg to predict an excretion of proteins > 0.5; 1.0 and 3.5 g/24 h.

Wahbeh *et al.*,[22] using benzethonium chloride for proteinuria and Jaffé kinetic for creatininuria in 50 Colombian outpatient nephrology patients, found a negative mean of the differences between PER and PCR. For the same values of PER of Leung (> 0.5; 1.0 and 3.5 g/24 h) they found cut-off values of PCR of 0.72; 1.2 and 3.23 g/g, respectively, with a kappa of 0.585, showing moderate strength of concordance between PER and PCR.

Montero *et al.*,[23] using the Jaffé kinetic method for creatinine and the turbidimetric method for

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proteinuria (Hitachi Modular DPP autoanalyzer), observed a direct and statistically significant correlation between PER y PCR in the second morning urine. For the whole group they found rho=0.91 but it was variable according to proteinuria, a situation that was also observed for the intraclass correlation coefficient (ICC). Their results for PER <300 mg/24 h were: rho=0.498, p<0.001, ICC=0.46; for PER=300-3499 mg/24 h, rho=0.828, p<0.001, ICC=0.66; and for PER > 3500 mg/24 h, rho=0.181, p=NS; ICC=0.18. These authors concluded that there was a good correlation between PCR and PER in the range of 300-3499 mg/24 h, that was less intense in values <300 mg/24h and that there was no correlation in the nephrotic range.

In the sample studied in the UNL, the kappa value, which measures the concordance in the assignment to categories A of the KDIGO 2012 classification according to PER and PCR, showed poor-slight strength when taking the value of 150 to divide the groups according to the two variables. The concordance strength increased to acceptable-considerable when the PCR value predictor of PER=150 mg/24 h, 82 mg/g was used, which in turn improved the assignment to categories A1 and A2. The number of students who would have been considered within the normal range of proteinuria taking the cut-off value of PCR=150 mg/g was lower; these false negatives should be reduced especially in the screening tests as is the case of PCR. The values of LR+=5.27 and LR-=0.12 found by the ROC analysis showed that the probability that the individual has proteinuria (PER?150 mg/24 h) is moderated if the VdC is exceeded and of not having it if the value is below thereof.

In the majority of studies found, the individuals are consecutively selected if they meet the inclusion criteria; these researches correspond to convenience samples according to the available individuals or pathologies. No other reports have been found that assess the concordance in the categorization A of the KDIGO 2012 by the two methodologies (in this range of proteinuria) or the variation in the strength of concordance using VdC for PCR. On the other hand, if the sample size increases it is possible that the 95 % CI of the kappa will become narrower. Extending the range of proteinuria to nephrotic values would increase the knowledge of the concordance of the two techniques in all categories A.

Conclusions

From the discussion arises that there are many variables still not controlled as methods of dosage of proteinuria and creatininuria, calibrators, sample used for measurement of PCR, etc. The majority of reports demonstrate variable correlations between PER and PCR for different ranges of proteinuria and find adequate sensitivities and specificities when PCR is used to predict PER, but the cut-off values vary widely among the different studies. The reagents for dosing proteinuria both in published articles and in clinical laboratories are various: pyrogallol red-molybdate, Coomassie brilliant blue, benzethonium chloride, salicylic acid, trichloroacetic acid, biuret, etc. The methods for the determination of creatinine are also varied: Jaffé, Jaffé kinetic (with or without compensation), enzymatic, etc. It is necessary to consider that the processing is sometimes manual and sometimes automatic, that the materials used to calibrate the urinary proteins are different in the absence of a unified calibrator and that the same sample is not always used for PCR (first or second morning urine, random urine and others).

The foregoing highlights the problem of using PCR=150 mg/g and PER=150 mg/24 h as equivalents to differentiate between normal and increased proteinuria. This can lead to errors in the diagnosis or prognosis of CKD regarding the categorization by stage A of proteinuria. Therefore, each laboratory should establish the cut-off value in order that PCR functions as a good screening test if it is desired to restrict the performance of proteinuria in 24 h-urine to the cases in which it is necessary.

Conflict of interest

All authors declare they do not have any conflict of interest.

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Contribution of the authors

Cecilia Brissón: conception and design of the article, analysis and interpretation of the data.

Verónica Cuestas: design of the article and acquisition and interpretation of the data.

Priscila Prono Minella, Rosina Bonifacino Belzarena: acquisition and interpretation of the data.

Susana Denner: analysis and interpretation of the data.

Verónica Fernández: conception of the article, interpretation of the data.

Silvia Marsili: interpretation of the data.

María Eugenia Brissón: design of the article.

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