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UTILITY OF THE PROTEINURIA /CREATINURIA RATIO IN KIDNEY DISEASE PATIENTS

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ABSTRACT

The 24-hour proteinuria has been considered, for a long time, to be the "gold standard" for the measurement of proteinuria; in order to diagnose and evaluate of the severity of many diseases. However, this assay method presents several constraints, notably those related to the difficulty of collecting the urine sample as well as its transportation to the laboratory, in addition to various physiological variations in protein excretion regarding the state of hydration, physical activity or even the postprandial period. Therefore, the evaluation of proteinuria using the ratio of proteinuria to creatinuria on a urine sample appears more than satisfactory in many situations, as an adequate alternative to the 24-hour proteinuria,

The final aim of our study was to find out if the collection of a urine sample and the calculation of the P/C ratio, could substitute a 24-hour urinary protein samples from kidney disease patients. All the tests were performed at the biochemistry laboratory, using the Alinity automated system (Abbott®).

The overall results show an excellent agreement between the two methods with a kappa coefficient of (0.91). This test, which is simpler, less expensive and has a shorter turnaround time, will also improve the time management of severe pathology, unlike the current situation where the 24-hour proteinuria result is known more than 24 hours after admission.

Keywords: Proteinuria, Creatininuria, Ratio, Kidney disease

INTRODUCTION

The value of proteinuria measurement in the diagnosis and evaluation of the severity of many diseases is well established. However, in ambulatory clinical practice, the determination of proteinuria in urine collected during 24 hours is not reliable, given the intra-individual variability of such an analyte in urine and the difficulties related to the various stages of the pre-analytical phase, from the collection to the transportation to the laboratory, even if the determination method were perfect.Therefore, the evaluation of proteinuria using the ratio of proteinuria to creatinuria on a urine sample appears more than satisfactory in many situations, as an adequate alternative to the 24-hour proteinuria, and it is so far considered the gold standard.

Our present study attempts to evaluate the concordance of the results of the two tests: the 24-hour proteinuria and the proteinuria calculated using the ratio (Proteinuria/Creatinuria) in order to determine the possibility of using the latter in our daily practice, instead of 24-hour proteinuria.

MATERIALS AND METHODS

This is a retrospective study from 01/12/2022 to 01/03/2023 where we collected the results of 146 24-hour urine samples from patients hospitalized in the Nephrology Department of the Ibn-Sina University Hospital in Rabat.

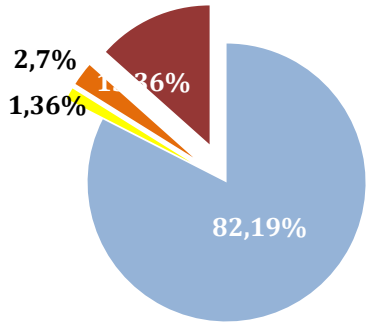
The 24-hour proteinuria was obtained by collecting all the urine of the patients over a 24-hour period. The collector noted the total volume, and a sample of it total, was collected for analysis. The determinations of Proteinuria and Creatinuria were performed at the Central Laboratory of Biochemistry of the same hospital. On the Abbott® Alinity-i system, total urinary proteins (in mg/l) were determined, by anautomated turbidimetric procedure in which benzethonium chloride is used as the protein denaturing, and then related to the 24h volume for the final result.

For the calculation of the ratio P/C, the same technique was used for the determination of total urinary protein, while creatinine (in mmol/l) was determined using the Jaffé colorimetric technique. The P/C ratio was obtained by the following calculation: Proteinuria (in g/l) divided by creatinuria (in mmol/l),the result is then presented in mg/mmol.
(**Ratio P/C** (mg/g) = (**proteinuria** (g/l) / **creatinuria** (mmol/ l) x **10**).

The concordance between the two methods, the 24-hour proteinuria and the ratio (P/C), was estimated using two statistical techniques with the help of the GRAPHPAD PRISM 9 software: the calculation of the correlation coefficient (kappa), followed by the Bland and Altman diagram. The latter is a graphical modelling by a cloud of points that represents the difference in average between two measurements. The two measurements are considered to be in concordance if the difference in means is within the interval (-2 SD (standard deviation); + 2 SD).

RESULTS

Of the 146 urine samples collected in our series, we found that, the average 24 h Proteinuria was: 382 mg/ 24H (Standard values are bellow: <150 mg/24H), while the Proteinuria/Creatinuria ratios had an average of 2,069.7 mg/g (Normal values :<300 mg/g).
120 of our patients (82.19%) had a simultaneous elevation of the 24-hour proteinuria and the proteinuria/creatinuria ratio, while two patients (1.36%) had a normal 24-hour proteinuria and a high proteinuria/creatinuria ratio. On the other hand, only four patients (2.7%) showed pathological 24-hour proteinuria with a proteinuria/creatinuria ratio within the norm. As for the remaining 20 subjects in our study (13.6%), their results were within physiological norms.(Fig:1)



	24Hour Proteinuria	Proteinuria/Creatinuria Ratio
82,19 %	*Pathological*	*Pathological*
13.6%	*Normal*	*Normal*
2,7%	*Pathological*	*Normal*
1,36%	*Normal*	*Pathological*

Figure 1: The results of both the 24H Proteinuria and the P/C ratio among the patients.

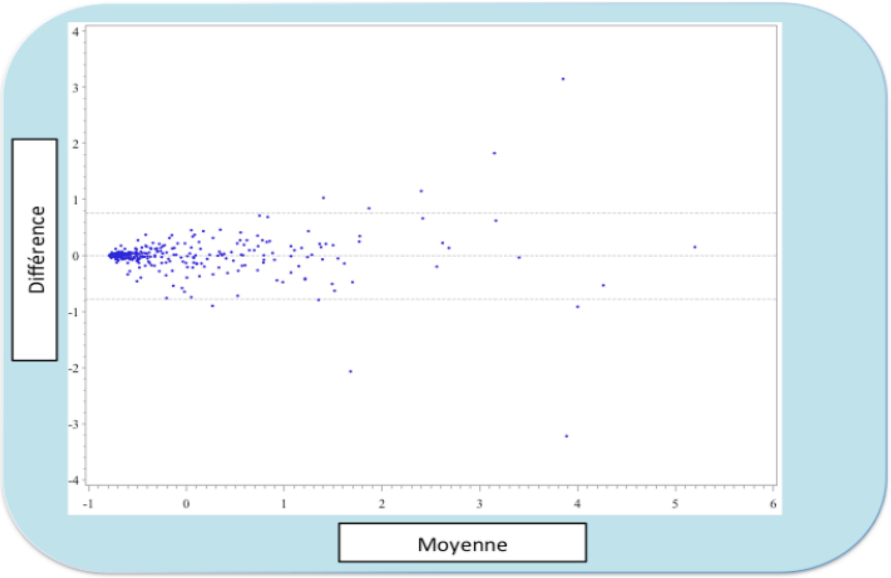


Figure 2: Bland et Altman diagram: Proteinuria/Creatinuria ratio vs the 24H Proteinuria (P24)

The intraclass correlation coefficient kappa between the P24 measurement and the CPR was 0.91 (95% CI = 0.88-0.92).The limits of agreement are modeled by the Bland and Altman diagram (Figure 1). The majority of values are between +2 SD and -2 SD.

DISCUSSION

LE « GOLD STANDARD »

The detection of an elevated protein value in the urine (proteinuria) is considered an independent risk factor for renal and cardiovascular disease and its measurement is recommended for the follow-up of individuals identified as being at risk of developing such pathologies. [1]

The 24-hour proteinuria assay has been considered, for a long time, as the gold standard for the measurement of proteinuria (9). However, this assay method presents several constraints, notably those related to the difficulty of collecting the urine sample as well as its transportation to the laboratory. [2]

In addition, there are various physiological variations in protein excretion, particularly in the postprandial period and according to the state of hydration or physical activity. It should be noted that one study showed that 24-hour urine samples could be considered incomplete in 10 to 20% of cases. [3]

EXPRESSION AS PROTEINURIA/CREATININURIA RATIO

The measurement of the protein to creatinine ratio, on a urine sample (Spot) has the advantage of being much easier and faster to perform. It also allows urine to be collected at any time of the day.The concordance between these two techniques, in our study, was evaluated by two different statistical methods: the calculation of the kappa correlation coefficient and the realization of the Bland and Altman diagram.(Fig:2) The concordance between two tests can be considered as good when the kappa correlation coefficient is higher than 0.6, and it is excellent if it is higher than (0.8).The overall results show an excellent agreement between the two methods with a kappa coefficient of (0.91). (CI 95% = 0.88-0.87)

Our results would appear to be consistent with two different studies conducted by NICE (National Institute for Health and Clinical Excellence) conducted by *Ruggementi* in 1998 [4] and by *Mac Gregor* in 2007, which showed good correlation results (>0.91). Other studies even presented the P/C ratio as better for predicting the occurrence of death or worsening of the disease than the 24-hour proteinuria [5].

The diagram we obtained shows that almost all the measurements are between the limits of agreement, which is similar to the results of two studies done in 2015 by Mouel et al [6]. Only 4 cases in our study were outside the standard deviations, out of the 146 patients studied, i.e. less than 3% of non-concordant results. Thus, this is an acceptable rate of mismatch, as no biological test is 100% valid. Our results seem to be similar to data from a French study performed in 2016 by B.Marine.[7]

The P/C ratio is widely mentioned in the recommendations of various learned societies internationally. In 2011, the recommendations of the French HAS (Haute Autorité de Santé) and the NICE (National Institute for Health and Clinical Excellence) in England [4], both of the organizations recommend that the detection of urinary protein excretion, should no longer be based on the measurement of proteinuria on a 24-hour urine collection,and conclude that the P/C ratio should be used as the first choice, given the ease, effectiveness and economy of its use. Australia and New Zealand [8] leave no doubt in their 2014 recommendations and refer only to P/C ratio as a diagnostic tool.

Other studies have also shown the correlation between the 24-hour proteinuria, and P/C ratio in different pathological situations. Indeed, a study conducted by Yin et al [9] demonstrated a correlation between the two tests in the context of predicting the occurrence of severe complications such as end-stage renal disease (ESRD) in a population of subjects with chronic kidney disease (CKD).

LIMITATIONS OF RCP

The major problem with the use of the P/C ratio is its very high intra-individual variability, which is all the more important as the protein concentration is low. This intra-individual variability of proteinuria, means that a positive result must always be confirmed by a second or even a third sample.Ideally, the second test should be performed under more favorable conditions, such as a sample from the first morning urine, which can exclude orthostatic proteinuria, a benign phenomenon; this makes the morning urine sample a much better choice than a random sample from the day or 24-hour urine [10].

It should also be remembered, that creatinine excretion depends on non-kidney related factors. It is important to keep this in mind when interpreting the P/C ratio, especially in elderly patients or subjects with low body and muscle mass. In fact, substitution of low creatinine in the denominator resulted in a significant increase in the ratio without showing pathological proteinuria [11].In these cases, it may be necessary to opt for measurements based on a 24-hour urine collection.Similarly, particular care is in order, and a second measurement or even a 24-hour urine collection may be recommended, for samples obtained from highly concentrated or, conversely, highly diluted urine.

CONCLUSION

It is obvious that our study is not on a large scale, but our sample size was sufficient to show statistically significant results in agreement with the literature.The final aim of our work was to find out if the collection of a urine sample and the calculation of the P/C ratio, could substitute a 24-hour urine collection.

Our results were all positive and consistent with the literature. Although a larger study, on a national; would obviously be more relevant in terms of the power of the statistical results, it seems to us thatthe P/C ratiocould be an alternative to the 24-hour proteinuria, as is already the case for monitoring chronic renal failure (recommended by the HAS).

This test, which is simpler, less expensive and has a shorter turnaround time, will reduce the number of unnecessary hospitalizations in the event of negative proteinuria on the P/C ratio, and will reduce the cost to public health. It will also improve the time management of severe pathology with a concomitant blood and urine test result, unlike the current situation where the 24-hour proteinuria result is known more than 24 hours after admission.

REFERENCES

1. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and strratification. Am J Kidney Dis 2002 ; 39 : S1-266.
2. Chitalia VC, Kothari J, Wells EJ, Livesey JH, Robson RA, Searle M, et al. Cost-benefit analysis and prediction of 24-hour proteinuria from the spot urine protein-creatinine ratio. Clin Nephrol 2001 ; 55 : 436-47
3. Mitchell SCM, Sheldon TA, Shaw AB. Quantification of proteinuria: a re-evaluation of the protein/creatinine ratio for elderly subjects. Age Ageing 1993; 22 : 443 9.
4. National Institute for Health and Clinical Excellence, National Collaborating Centre for Chronic Conditions. Chronic kidney disease. National clinical guideline for early identification and management in adults in primary and secondary care. London: Royal College of Physicians; 2008.
5. ethven S, MacGregor MS, Traynor JP, Hair M, O'Reilly DSJ, Deighan CJ. Comparison of urinary albumin and urinary total protein as predictors of patient outcomes in CKD. YAJKD 2011 ; 57 : 21-8.
6. D.journois, Concordance de deux variables : l'approche graphique : Méthode de Bland et Altman, 2004, Revue des maladies respiratoires 21(1):127–130
7. Belhadia Marine, Evaluation de la concordance statistique du ratio protéinurie/créatininurie, en comparaison de la protéinurie des 24 heures, chez les patientes pré-éclamptiques, Université de Bordeaux 2 – Victor Segalen, 2016, N°3178
8. Lowe SA, Bowyer L, Lust K, McMahon LP, Morton M, North RA, et al. SOMANZ guidelines for the management of hypertensive disorders of pregnancy 2014. Aust N Z J ObstetGynaecol. 1 oct 2015;55(5):e1-29
9. Ying T, Clayton P, Naresh C, Chadban S. Predictive value of spot versus 24-hour measures of proteinuria for death, end-stage kidney disease or chronic kidney disease progression. BMC Nephrology 2018 ; 19 : 55-63
10. Shah VP, Midha KK, Findlay JW, Hill HM, Hulse JD, McGilveray IJ, et al. Bioanalytical method validation - a revisit with a decade of progress. PharmRes 2000 ; 17 : 1551-7.
11. Shah VP, Midha KK, Findlay JW, Hill HM, Hulse JD, McGilveray IJ, et al. Bioanalytical method validation - a revisit with a decade of progress. PharmRes 2000 ; 17 : 1551-7.