Urinary protein/creatinine ratio versus 24-hour proteinuria in the evaluation of lupus nephritis

Relação proteína/creatinina na urina versus proteinúria de 24 horas na avaliação de nefrite lúpica

Authors

Grace Tamara Moscoso Solorzano[1]
Marcus Vinicius Madureira e Silva[1]
Sílvia Regina Moreira[3]
Sonia Kiyomi Nishida[4]
Gianna Mastroianni Kirsztajn[1]

[1]Glomerulopathy sector at Universidade Federal de São Paulo – UNIFESP.
[2]Central laboratory of *Hospital do Rim*.
[3]Laboratory of Glomerulopathy and Renal Immunopathology of the Glomerulopathy sector at UNIFESP.

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Correspondence to:
Gianna Mastroianni Kirsztajn
Setor de Glomerulopatias, Disciplina de Nefrologia, UNIFESP-EPM
Rua Botucatu, 740
São Paulo – SP – Brasil
Zip code 04023-900
E-mail: giannamk@uol.com.br

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ABSTRACT

Introduction: The urinary protein/creatinine ratio has been used instead of 24-hour proteinuria in Nephrology practice for the follow-up of glomerular diseases, considering the advantages of collection and the low cost. However, there are still doubts as to its applicability both for an isolated evaluation and for the follow-up of patients with lupus nephritis. **Objective:** To evaluate 24-hour proteinuria determinations and random urine samples, performing urinary creatinine correction and urinary protein/creatinine ratio in subjects with lupus nephritis. **Methods:** 24-hour proteinuria and urinary protein/creatinine ratio were determined by conventional methods (automated Pyrogallol for proteinuria and alkaline picrate for creatinine). **Results:** Seventy-eight urine samples of 41 patients diagnosed with systemic lupus erythematosus, according to the American Rheumatology Association, with lupus nephritis, were analyzed, and a good correlation between 24-hour proteinuria and urinary protein/creatinine ratio ($r = 0.9010$ and $r^2 = 0.813$) was observed. However, a poor correlation between random proteinuria (without creatinine correction) *versus* 24-hour proteinuria ($r = 0.635$ and $r^2 = 0.403$) or *versus* urinary protein/creatinine ratio ($r = 0.754$ and $r^2 = 0.569$) was seen. **Conclusion:** 24-hour proteinuria and urinary protein/creatinine ratio were useful in the follow-up of each case. However, we observed that the absolute values were different, which did not allow the replacement of one for the other during follow-up, especially when this result is used to define the activity of the disease. Based on these results, we suggest

RESUMO

Introdução: Tem-se defendido a utilização do índice urinário proteína e creatinina em substituição à determinação de proteinúria de 24 horas para acompanhamento de doenças glomerulares, considerando-se as vantagens de maior facilidade na coleta e o menor custo. Entretanto, há dúvidas quanto à pertinência de usar este índice tanto numa avaliação isolada como no seguimento de pacientes com nefrite lúpica. **Objetivo:** Avaliar as determinações de proteinúria de 24 horas e proteinúria em amostra isolada de urina, fazendo a correção pela creatinina urinária, relação proteinúria/creatininúria, em indivíduos com nefrite lúpica. **Métodos:** Determinações de proteinúria de 24 horas e relação proteinúria/creatininúria por métodos convencionais (Pirogalol automatizado para proteinúria e picrato alcalino para creatinina). **Resultados:** Foram comparadas 78 amostras de urina de 41 pacientes com diagnóstico de lúpus eritematoso sistêmico, segundo os critérios da Associação Americana de Reumatologia, com nefrite lúpica, constatando-se uma boa correlação entre proteinúria de 24 horas e relação proteinúria/creatininúria ($r = 0{,}9010$ e $r^2 = 0{,}813$). Não se observou, entretanto, uma boa correlação entre proteinúria em amostra isolada (sem correção pela creatinina urinária) *versus* aquela de 24 horas ($r = 0{,}635$ e $r^2 = 0{,}403$) ou *versus* relação proteinúria/creatininúria ($r = 0{,}754$ e $r^2 = 0{,}569$). **Conclusão:** Os marcadores de proteinúria de 24 horas e relação proteinúria/creatininúria isoladamente mostraram-se úteis no acompanhamento de cada caso. Porém, observou-se que os seus valores absolutos são diferentes, não possibilitando a substituição de um pelo outro ao longo do seguimento, particularmente quando este resultado é usado para definição de atividade da doença. Se necessário, sugere-

a period of intersection from one to the other (two to three determinations by both methods) and the choice of one marker for proteinuria follow-up, if necessary.
Keywords: Lupus Nephritis. Proteinuria. Lupus Erythematosus, Systemic. Diagnostic Tests, Routine.

se um período de intersecção (duas a três determinações pelos dois métodos) para mudança de um para outro e escolha de um único marcador preferencial para seguimento da proteinúria.
Palavras-chave: Nefrite Lúpica. Proteinúria. Lúpus Eritematoso Sistêmico. Testes Diagnósticos de Rotina.

Introduction

The quantification of proteinuria is a valuable test to analyze kidney diseases, thus being considered as a diagnostic and prognostic marker, besides being essential for the follow-up of treatments for glomerulopathy.

Gold standard is 24-hour proteinuria (24hP), due to the great variation in the concentration of urinary protein throughout the day – for different reasons –, which impedes the dosage in a random sample.

However, it is worth to mention that 24hP determination is associated with some difficulties, such as patient adherence and the adequate collection and handling of this material in the laboratory.

In the past few years, the use of protein/creatinine ratio has been spread in random urine samples as a proper test for the quantification of proteinuria.[1] It has been demonstrated that P/C ratio is an accurate and reliable method to estimate the protein in the urine of pregnant women, kidney-transplanted patients and those with diabetic nephropaty, as well as in children.[2-6] However, there are doubts as to the reliability to use this index both for the isolated evaluation and for the follow-up of patients with lupus nephritis.

In this study, 24hP determinations and random urine samples were analyzed with the urinary creatinine correction by the P/C ratio in patients with lupus nephritis. The objective was to evaluate the possibility that the second test can replace the first one for the follow-up of these patients.

Material and methods

Forty-one patients in the outclinic patient of glomerulopathies at *Universidade Federal de São Paulo* (UNIFESP) with systemic erythematosus lupus were evaluated according to the criteria of the American Association of Rheumatology. They all had clinical and laboratory diagnosis of lupus nephritis; eight did not have a biopsy (six patients) or the material was not adequate (two patients); the others had lupus nephritis classified according to the World Health Organization (WHO) in classes III (3), IV (18), V (11) and VI (1). One patient underwent two renal biopsies during follow-up (the first showed class V, and the second, class IV, but here we considered class V). Other characteristics of the studied population are demonstrated in Table 1.

Patients collected 24-hour urine samples for examinations and, when delivering this material to the laboratory, they collected an additional random urine sample.

In order to determine 24hP and proteinuria in a random urine sample, the automated Pyrogallol method was used; urinary creatinine was measured by the alkaline picrate method. Besides the tests in this protocol, patients underwent the examinations for the routine evaluation of their disease.

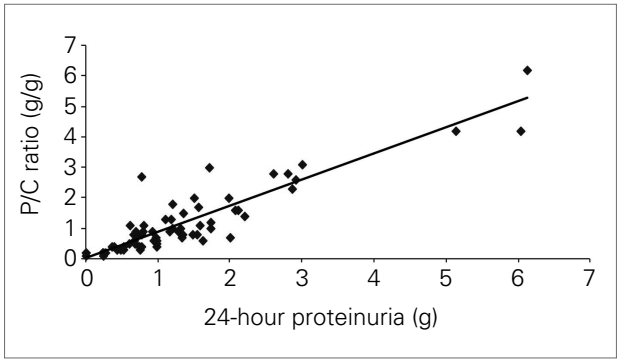
Table 1 Demographic characteristics, diagnostic criteria for lupus and comorbidities of patients with lupus nephritis

Characteristics	Mean	n	Minimum-Maximum
Age	48 years		18 to 78 years
Gender (F/M)		36/5	
Skin color	White	27	
	Brown	9	
	Blacl	5	
N. of diagnostic criteria for SLE	Mean 6		4 to 9
Time of diagnosis	Mean 9.2 years		2 months to 26 years
Associated *diabetes mellitus*		2	
Arterial hypertension		26	

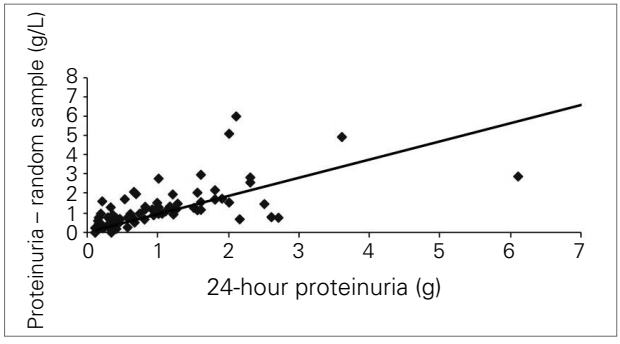
Table 2 Minimum, maximum, median and mean values of proteinuria (in a random urine sample, with and without creatinine correction, and 24 hours) in 78 examinations

Proteinuria	Median	Minimum	Maximum	Mean
Proteinuria (random sample, g/L)	0.8	0.1	7.4	1.1
Protein/creatinine ratio (random urine sample, g/g)	0.8	0.1	6.2	2.9
24-hour proteinuria (g)	1.0	0.0	6.1	2.4

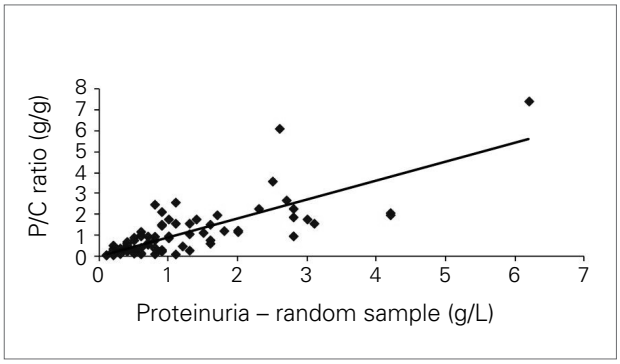
Graph 1. Correlation between 24-hour proteinuria and protein/creatinine ratio in a random urine sample (n = 78, r = 0.901).



Graph 2. Correlation between 24-hour proteinuria and proteinuria in a random sample (n = 78, r = 0.635).



Graph 3. Correlation between proteinuria in a random sample and protein/creatinine ratio in a random urine sample (n = 78, r = 0.754).



Results

Patients with lupus nephritis presented with mean serum creatinine of 1.0 mg/dL (minimum: 0.7; maximum: 4.7 mg/dL). Proteinuria values are presented in Table 2.

Seventy eight urine samples of patients with lupus nephritis were compared, showing a good correlation between 24hP and P/C ratio (r = 0.901 and r^2 = 0.813, Graph 1). When comparing values of proteinuria in a random sample with 24hP (r = 0.635 and r^2 = 0.403, Graph 2), and with the P/C ratio (r = 0.754 and r^2 = 0.569, Graph 3), the correlation between variables was lower.

Discussion

It is important to consider that 24hP remains as gold standard to diagnose proteinuric diseases, and it is the most used parameter for syndromic definitions concerning glomerular diseases. The P/C ratio in a random urine sample is a simple test, which is low-cost and easy to perform. It does not require timed collection of urine, since it can be collected any time of the day, although there are some controversies as to the quality of the sample. Some problems were found concerning the use of this examination: the lack of knowledge on its applicability and, from the practical point of view, the frequent inexistence of specific codes in clinical laboratories to facilitate its performance, when ordered by the doctors.

Even though it is hard for nephrologists to understand how difficult it is to provide an examination that depends only on dividing the result of protein dosage in a urine sample by the result of creatinine in the same sample, using the same measurement, apparently it is not possible to charge for such examination in most national laboratories, since it is not part of the list of examinations performed by health insurance companies.

Since this argument is frequently used as a reason, it is possible to display its importance together with some simple measures that can facilitate the

availability of this examination with time. The authors believe that some factors can contribute with the inclusion of this test in the laboratories: the personal contact between the assistant doctor and the clinical pathologist; the repetition of requirements to determine protein/creatinine ratio due to the need to count on this examination; and, in the first stage, the additional requirement of separate doses of protein and creatinine in the random urine sample (together with the order for protein/creatinine ratio, emphasizing the need to insert the calculation of this ratio), as collaboration, to facilitate charging for these examinations. In order to interpret the results, it is worth to mention the values in this marker, which are used to define response to treatment, for example, are similar to the ones used for 24hP; results between zero and 0.2, or 0.3 g/g[2] are considered normal.

In this study, a great correlation between 24hP and P/C ratio was observed in a random sample among patients with lupus nephritis, which is in accordance with prior studies performed with other subgroups (pregnant women, kidney transplanted patients and patients with diabetic nephropathy).[2-4,6] For instance, Khan *et al.*[6] noticed an excellent correlation ($r = 0.96$, $p < 0.001$) between both parameters among patients with kidney diseases, and not such a good one with proteinuria in a random sample without urinary creatinine correction (0.52), whose use may define errors of interpretation of proteinuria in the clinical context.

In the group of lupus nephritis, it is possible to say that every marker, alone, was useful to determine proteinuria. However, absolute values of both exams were different in each case, which did not enable the replacement of one for the other during follow-up, especially when this result should be used to define the activity of the disease, particularly such polymorph glomerular disease lupus nephritis.

Because of that, if it is necessary to replace one test for the other during follow-up of a specific patient, the suggestion is a period of intersection (two to three determination by both methods) before any change is defined.

Finally, it is important to say that the isolated collection of the random urine sample to determine the P/C ratio has some advantages concerning facility, reliability, accuracy, and diagnostic speed; it could also be used as the preferential marker in subgroups of subjects with more difficult to properly collect urine in 24 hours, such as children, elderly patients and those with intellectual disabilities; or when the collection is incompatible with the professional activities of the patient, in case of refusing to do this examination or at the suspicion of lack of adherence.

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