Spot urine protein/creatinine ratios are unreliable estimates of 24 h proteinuria in most systemic lupus erythematosus nephritis flares

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The diagnosis of glomerulonephritis flares in systemic lupus erythematosus (SLE) is usually based on whether the magnitude of proteinuria has changed. Our study tests two methods to assess proteinuric change: protein/creatinine (P/C) ratios of intended 24-h urine collections or that of spot urine samples. Sixty-four patients with glomerulonephritis due to SLE followed in the Ohio SLE Study provided bimonthly paired spot and intended 24-h urine collections. Completeness of each collection was estimated as the ratio of the measured creatinine to the expected creatinine based upon Cockroft–Gault. Intended 24-h urine collections with measured/expected creatinine ratios between 0.5 and 0.9 (237 samples overall) showed ratios that were not significantly different from ratios of complete 24-h urine collections with ratios of 0.9–1.1 (159 samples). To compare spot and 24 h P/C ratios, we randomly selected pairs of samples with measured/expected ratios above 0.75. Consistent with previous studies, spot and 24-h urine P/C ratios showed good correlation over the range of values as well as reasonably strong concordance. Over the range of most SLE glomerulonephritis flares, however, correlation was present but concordance was poor. Our work suggests that the use of spot urine P/C ratios will yield more false-positive and -negative diagnoses of glomerulonephritis flares in patients with SLE than the ratio in 24-h urines.

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In chronic kidney disease, proteinuria magnitude is the strongest single predictor of glomerular filtration rate decrease.[1–3] Furthermore, therapy that reduces proteinuria slows glomerular filtration rate decrease. For example, glomerular filtration rate decrease is slowed by 1–2 ml/min/year for each therapy-induced 1.0 g/day reduction in proteinuria achieved by 4–6 months therapy.[3–6] Thus, accurate assessment of proteinuria trends is important in chronic kidney disease management.[6–8]

In systemic lupus erythematosus (SLE) glomerulonephritis (GN), accurately assessing proteinuria change is especially important. For SLE patients whose baseline proteinuria is <250 mg/day, proteinuria increases of 1.0[9–17] or $\geqslant 2$ g/day[18,19] are regarded as evidence of SLE GN flare, and mandate a prompt increase in steroid or immunosuppressive therapy.

The gold standard to assess proteinuria change is the protein content of an accurately collected 24-h urine (24-h proteinuria).[6,20] However, 24-h urine testing is a chore for the patient, and a nuisance for the physician because for each collection it must be determined whether it is a complete 24-h collection.[6] Random single-void (spot) urine testing was introduced in an effort to streamline further quantitative proteinuria assessment. Kidney Disease Outcomes Quality Initiative guidelines now recommend replacing 24-h urine testing with the protein/creatinine (P/C) ratio of random spot urine collections.[20] This recommendation is based on the many studies showing a high correlation coefficient between spot urine P/C ratios and 24-h proteinuria.[7,20–30] However, as we have previously pointed out, the high correlation coefficients are mainly the mathematical consequences of comparing these variables over a wide range.[6] Over more restricted, but clinically relevant ranges (e.g., 24-h urine P/C ratios 0.5–3.0), inspection of the graphical displays of the previous reports show only weak agreement between spot P/C ratio and 24-h proteinuria.[8,21,24–26,28–31] However, the previous reports either did not acknowledge or did not discuss its clinical significance.

This study is the first to assess the relationship between spot and 24-h urine P/C ratios when the goal is to assess proteinuria change over the 24-h proteinuria range of 0.5–3 g/day, the range of most SLE GN flares.[9,11,16,17,32] As we have discussed previously,[6,7] there is evidence that in proteinuric

chronic kidney disease, spot urine P/C ratio varies over a severalfold range during any given 24-h period, and the pattern of variability changes from day to day. Thus, the key question is whether a spot urine is a large enough sample from which to reliably estimate moderate changes in 24-h proteinuria. Our results show that it is not. However, the P/C ratio of an intended 24-h urine that is $\geqslant$50% complete is a reliable estimate of 24-h proteinuria. On this basis, we suggest that a reexamination of the use of spot urine P/C ratio to monitor SLE GN flare is warranted.

RESULTS

Table 1 shows the baseline demographics of the 64 OSS SLE GN patients studied herein. The majority are young female subjects with normal or nearly normal serum creatinine levels.

Expected 24-h urine creatinine levels (E) were calculated and compared with the measured creatinine levels (M) to determine the completeness of a 24 h collection (the M/E ratio). To evaluate whether body size influenced this determination, the relationship between M/E and body mass index was assessed by analysis of variance applicable to repeated measures, where body mass index was used as the predictor and M/E as the response, and subjects were used as a random effect. This analysis showed a statistically significant ($P<0.0001$) but weak relationship; the correlation coefficient between the two variables was -0.39, indicating that the body mass index explained only 16% of the variation in the M/E ratio. Thus, M/E ratios outside the range of 0.9–1.1 mostly reflected inaccurate 24-h collections, with high M/E ratios representing over collections, and low M/E ratios representing under collections.

To assess if completeness of an intended 24-h urine collection influenced the P/C ratio of the collection, we first examined the relationship between M/E ratio and P/C ratio for all 645 intended 24-h urine collections from the 64-patient cohort (Figure 1a). Using analysis of variance applicable to repeated measures where M/E ratio was used as the predictor and log (24-h P/C ratio) as the response, and subjects as random effects, no relationship between M/E ratio and P/C ratio was found ($P=0.11$).

To examine further the relationships shown in Figure 1a, a subset analysis was performed comparing the P/C ratios in each of the following M/E ratio categories: 0.5 to <0.75, 0.75 to <0.9, 0.9–1.1, and >1.1 (Figure 1b). M/E ratios of <0.5 were not assessed because of very few values. To mitigate the possible confounding effect of overrepresentation by a few individuals with low M/E ratios but high P/C ratios, only data from patients contributing to at least two of these M/E ratio categories were used. This resulted in 544 24-h urine P/C ratios from 50 patients. No differences were found among the P/C ratios of the four M/E categories, using analysis of variance applicable to repeated measures, with M/E category as a fixed effect and subjects as random effects ($P=0.11$). These data suggest that the P/C ratio of an intended 24-h urine collection with an M/E ratio >0.5 is a reliable estimate of the P/C ratio of a complete 24-h collection. This analysis also reveals the intraindividual variability of 24-h collections, with 15 patients contributing to two M/E ratio categories, 23 patients to three categories, and 12 patients to four categories.

For the primary comparison of paired spot to 24-h urine P/C ratio, we chose the pairs in which the M/E ratio of the intended 24-h urine was $\geqslant$0.75. This was done to increase the reliability with which the intended 24-h urine P/C ratio estimated the P/C ratio of a complete 24-h collection. The

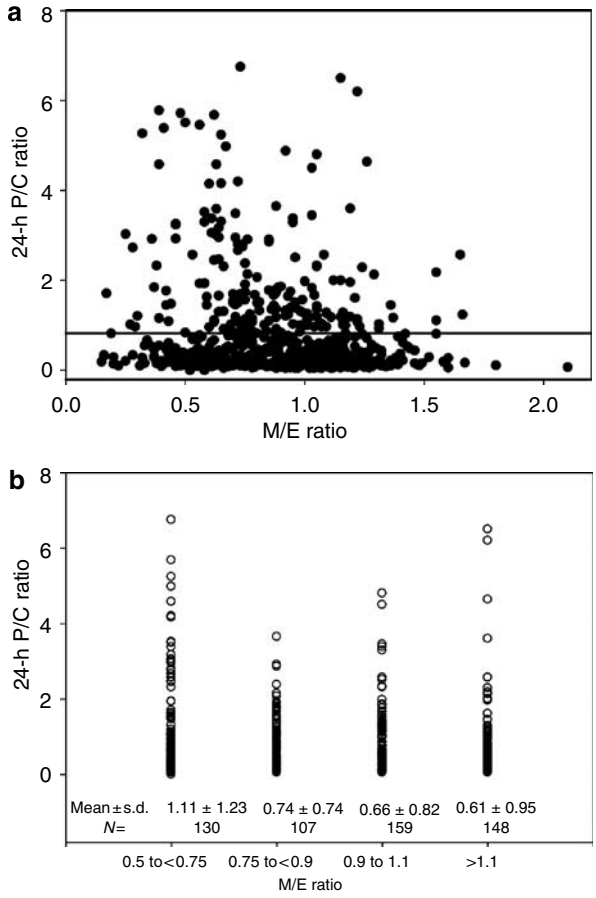

Figure 1 | Intended 24-h urine collections that are greater than 50% complete provide p/c ratios comparable to that of complete 24-h urine collections. (**a**) The relationship between M/E ratio and 24-h urine P/C ratio for each of the 645 individual 24-h collections of the OSS patients. These values are shown in relationship to the mean 24-h P/C ratio (horizontal line). No relationship between M/E ratio and P/C ratio was found. ($P=0.11$). (**b**) Individual mean 24-h urine P/C ratios by M/E ratio group are shown. No differences were found among the P/C ratios of the four M/E ratio categories ($P=0.11$).

Table 1 | Baseline demographic and clinical characteristics of the SLE GN patients

N	Age[1]	Sex[2]	Race[3]	Protein/creatinine[1]	Serum creatinine[1]
64	34 ± 10	60/4	24/35/5	1.8 ± 2.4	1.2 ± 0.7

GN, glomerulonephritis; SLE, systemic lupus erythematosus.
[1]Mean ± s.d. at baseline.
[2]Female/male.
[3]African-American/Caucasian/other.