Relationship between Albuminuria and Total Proteinuria in Systemic Lupus Erythematosus Nephritis: Diagnostic and Therapeutic Implications

Daniel J. Birmingham,* Brad H. Rovin,* Ganesh Shidham,* Michael Bissell,† Haikady N. Nagaraja,‡ and Lee A. Hebert*

Departments of *Internal Medicine, †Pathology, and ‡Statistics, Ohio State University, Columbus, Ohio

Background and objectives: Albuminuria is regarded a sensitive measure of progression of glomerular disease. This study was undertaken in patients who had systemic lupus erythematosus glomerulonephritis (n = 57) and were followed in the Ohio SLE Study to determine whether measuring albuminuria offered clinical advantages over that of total proteinuria.

Design, setting, participants, & measurements: Twenty-four-hour urine collections (n = 127) were obtained at baseline and annually for measurement of microalbumin, total protein, and creatinine.

Results: There was a strong linear relationship between microalbumin-creatinine and protein-creatinine ratios over the entire range of protein-creatinine ratios; however, in the protein-creatinine ratio range 0.0 to 0.3, as the protein-creatinine ratio increased, the microalbumin-protein ratio increased much more than the protein-creatinine ratio. Also, the greater the protein-creatinine ratio, the greater was the evidence for nonselective proteinuria (protein-creatinine ratio – microalbumin-creatinine ratio).

Conclusions: For the diagnosis of proteinuria renal flare, measuring albuminuria offers no advantage over measuring total proteinuria because changes in protein-creatinine and microalbumin-creatinine ratios are highly correlated over the designated ranges for systemic lupus erythematosus glomerulonephritis proteinuric flares. In those with normal-range proteinuria, subsequent changes in microalbumin-protein ratio might be a better forecaster of renal flare than changes in protein-creatinine or microalbumin-creatinine ratio. High protein-creatinine ratios are associated with evidence of nonselective proteinuria, which may increase the nephrotoxicity of proteinuria. Thus, using high-threshold criteria for systemic lupus erythematosus flare (allowing greater proteinuria increase before flare is declared) may expose the kidney to greater nephrotoxicity than using the low-threshold criteria for systemic lupus erythematosus flare.


G lomerular injury usually induces an increase in glomerular permeability to macromolecules, resulting in increased urinary excretion of plasma proteins. Under conditions of severe glomerular injury, albumin (molecular weight approximately 69 kD) is the most abundant protein excreted in the urine, generally accounting for much more than 50% of the urinary proteins (1). Thus, albuminuria is the hallmark of glomerular proteinuria; however, under conditions of mild glomerular injury, albumin usually comprises much less than 50% of urinary proteins (1). The low rate of albuminuria compared with that of total proteinuria (albumin + nonalbumin proteinuria) in mild glomerular injury is thought to be the result, at least in part, of the greater capacity of the renal tubules to absorb filtered albumin compared with that of larger proteins such as IgG (molecular weight approximately 150 kD) (2–4). Hereafter, “total proteinuria” is referred to as proteinuria.

The prime example of using albuminuria to monitor progression of early glomerular injury is in diabetic glomerulosclerosis, where increases in albuminuria are indicative of progression of diabetic glomerulosclerosis, even when the proteinuria rate is within the normal range (e.g., <200 mg/24 h) (5–8). For measurement of low-level changes in albuminuria, immunoassays have been developed to detect urine albumin in concentrations <1 mg/dl. These are referred to as “microalbumin” assays (1). Normal 24-h urine albumin excretion by these assays is <30 mg albumin/g creatinine (8). Albuminuria rates of 30 to 300 mg/g creatinine are referred to as “microalbuminuria.” Albuminuria rates beyond that range are referred to as “macroalbuminuria” (8). When the macroalbuminuria range is reached in diabetic nephropathy, albumin becomes the dominant urinary protein and proteinuria parallels albuminuria. At that point, the advantage of measuring albuminuria over proteinuria is generally lost (7).

It is well established that in chronic kidney disease (CKD), albuminuria and proteinuria are highly correlated (7–9), particularly when 24-h proteinuria exceeds 500 mg (7); however, in systemic lupus erythematosus glomerulonephritis (SLE GN),
the relationship between proteinuria and albuminuria has not been rigorously examined (10–12). It is plausible that albuminuria–proteinuria relationships are different in SLE GN compared with that of other forms of CKD. Mechanisms that could account for such differences include the following: (1) The microalbuminuria assay does not detect intact albumin that has been modified in vivo. The latter process is particularly common in patients with diabetes and CKD (13). The extent to which albumin is modified in SLE is unknown. (2) Albumin that undergoes glomerular filtration in CKD is extensively absorbed by the renal tubules. The fraction of albumin that is not absorbed undergoes extensive degradation, apparently by proximal tubular lysosomes, with excretion in urine as low molecular weight peptides <10 kD. These peptides are not measured by the immunoassay for microalbuminuria or by the usual clinical measures of proteinuria such as pyrogallol red or Coomassie blue (4,13,14). In experimental models of GN, renal tubular degradation of albumin does not occur (13,14). Thus, intact albumin could be overrepresented in SLE GN urine compared with that of CKD urine. (3) There is evidence from experimental models that some conditions of moderate albuminuria may be entirely the result of failure of renal tubular retrieval of albumin that normally is filtered by the normal glomerulus (15,16). Renal tubular albumin retrieval could differ between SLE and other CKD conditions. (4) Hypoalbuminuria independent of urine protein loss commonly occurs in SLE. The apparent mechanism is inflammation-induced albumin catabolism (17). This mechanism could influence albuminuria–proteinuria relationship in SLE GN compared with that of other causes of CKD in which inflammation is not a prominent feature. This study explores the relationship between albuminuria and proteinuria in patients with SLE GN across a wide range of proteinuria, including threshold ranges that commonly are used for identifying SLE proteinuric flares.

Materials and Methods

This study involved 57 patients who had SLE GN and were screened for or followed in the Ohio SLE Study (OSS) (18), a research protocol approved by the Ohio State University institutional review board and that required informed written consent for participation and is in adherence to the Declaration of Helsinki. Each patient underwent kidney biopsy. This showed 5% with World Health Organization (WHO) class II, 19% with class III, 44% with class IV, and 32% with class V. For those who were followed in the OSS, 24-h testing for protein and creatinine was done bimonthly (18). Annually, testing for microalbuminuria was included in the 24-h testing regimen.

For assessment of the diagnostic usefulness of albuminuria compared with proteinuria in assessing SLE proteinuric flare, regression of albumin (A)-creatinine (C) ratio on protein (P)-C ratio was examined in relationship to the previously published criteria for SLE GN proteinuric flare. These criteria can be organized into three general categories, as follows: Low-threshold criteria for the diagnosis of proteinuric SLE flare are those reported by the OSS (18), the LJP 394 Study (19), and the British Isle Lupus Assessment Group (BILAG) Category B renal flare (20). In the cited studies, the minimum increase in proteinuria that qualifies as a proteinuric renal flare are OSS (24-h urine P-C ratio increasing from <0.5 to ≥1.0) (18), LJP 394 (24-h proteinuria increasing by 800 mg along with corroborative changes in urine sediment [19]), and BILAG category B (24-h proteinuria of >1.0 g, increasing by >50 but <100% [20]). The intermediate threshold criterion is that of BILAG category A renal flare (proteinuria increasing from <0.2 to >1.0 g/24 h) (21). The high threshold criteria are those reported by Moroni et al. (22), Ioannidis et al. (23), Illei et al. (24), Mosca et al. (25), and Mok et al. (26).

In those studies, the minimum increase in proteinuria that qualified as an SLE proteinuric flare was, in a patient with 24-h proteinuria <2.0 g, an increase in 24-h proteinuria of ≥2.0 g/24 h.

In the OSS, proteinuria and albuminuria rates are expressed as the P-C ratio or the A-C ratio of intended 24-h urine collection. This was done to adjust for inaccuracies in the collection of the intended 24-h urine collections (27,28). To convert the 24-h protein excretion rates of the other cited studies (18–26) to 24-h P-C ratios, we divided the 24-h proteinuria values used for each of the flare criteria by 1.3. The latter value is the mean 24-h urine creatinine excretion in the OSS patients with SLE GN based on 645 consecutive intended 24-h urine collections (28).

Analytic Studies

All analyses were performed in the laboratories of the Ohio State University Medical Center. Urine protein was measured by an automated pyrogallol red method (29), coefficient of variation (CV) 3.3% at control level 71.6 mg/dl. Urine creatinine was measured by an automated picric acid method CV 2.8%, control level 79.0 mg/dl. Microalbuminuria was measured by immunoassay CV 0.7%, control level 9.4 to 13.5 mg/dl.

Statistical Analysis

All mean values are ±1 SD. The relationship between albuminuria or nonselective proteinuria and total proteinuria was examined by linear regression.

Results

The baseline clinical characteristics of the 57 patients were mean age of 34.4 ± 10.8 yr; 91% female; 64% European American, 33% African American, and 3% other races; mean serum creatinine of 1.11 ± 0.6 mg/dl; mean 24-h urine P-C ratio 1.51 ± 2.36; mean C3 98 ± 39 mg/dl; mean C4 17 ± 12 mg/dl. At baseline, therapy included prednisone in 52 (91%) of 57, an immunosuppressive (mycophenolate, azathioprine, or cyclophosphamide) in 50 (88%) of 57, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker in 31 (54%) of 57. All of the patients with abnormal proteinuria (P-C ratio >0.2) were receiving either an ACEI or an angiotensin receptor blocker. Other therapies that can influence proteinuria (30) either were not used (e.g., nonsteroidal anti-inflammatory drugs) or were used in too few patients to influence this study. Specifically, statins were received by eight patients, non-dihydropyridine calcium channel blocker by one patient, and dihydropyridine calcium channel blocker by five patients. A total of 127 baseline and annual 24-h urine collections were tested for protein, microalbumin, and creatinine. The median number of 24-h urine collections tested per patient was 2.0.

Figure 1 shows the relationship between the P-C ratio and A-C ratio for each of the 24-h urine collections. As shown, P-C and A-C were linearly related and highly correlated (r = 0.99, slope = 0.79, P < 0.0001). Shown in relationship to the regression of A-C on P-C is the minimum increase in proteinuria
required to diagnose SLE proteinuric flare by the low- (18,19), intermediate- (19,20), and high-threshold criteria (22–26).

To explore further the informative value of albuminuria measurements, we examined the relationship between 24-h urine P-C ratio and the corresponding A-P ratio (the proportion of urine protein that is immunoassayable albumin). This relationship is shown in Figure 2 over the entire range of 24-h urine P-C ratios (Figure 2A) and over the range of P-C ratios <1.8 (Figure 2B). The data in Figure 2 indicate that as proteinuria increases from normal to higher levels, the A-P ratio increases more rapidly than the P-C ratio, until a P-C ratio of approximately 0.3 is reached. Thereafter, the A-P ratio plateaus.

There is considerable evidence that proteinuria itself is nephrotoxic, particularly nonselective proteinuria (reviewed in references [30,31]). In this study, we estimated the magnitude of nonselective proteinuria as P-C ratio – A-C ratio. This parameter is shown in relationship to P-C ratio in Figure 3. As shown, the greater the P-C ratio, the greater is the magnitude of A-C ratio – P-C ratio (r = 0.86, slope = 0.21, P < 0.0001). There was no relationship between the patients’ renal biopsy WHO classification (determined at study baseline) and the proteinuria relationships described (determined at baseline, during OSS follow-up [up to 4 yr]), or both.

**Discussion**

This study is the first to examine in detail the relationship between albuminuria and proteinuria in SLE GN. The comparison of albuminuria with proteinuria was based on annual testing and without regard to the patient’s proteinuria status. Thus, this analysis is not a longitudinal assessment; however, we suggest that it is a rigorous cross-sectional assessment of the relationship between albuminuria and proteinuria in SLE GN because each segment of the regression of A-C on P-C ratio is represented by multiple patients (the median measure per patient is 2.0), and the principal therapies that most influence proteinuria (ACEI, angiotensin receptor blocker) were uniformly used in the patients with abnormal proteinuria. Thus, we suggest that the shape of the cross-sectional relationships shown in Figures 1, 2, and 3 are representative of the expected longitudinal relationships of these parameters.

We found no correlation between the albuminuria/protein-
Proteinuric events reported in this study occurred previously tested by the study protocol because kidney biopsy gen-
eria relationships of this study and the study patients’ kidney biopsy WHO classification; however, this issue was not rigor-
ously tested by the study protocol because kidney biopsy gen-
erally was done at or before entry into the OSS, and most of the
proteinuric events reported in this study occurred ≥1 yr after
study entry. Because WHO class changes with therapy, we can-
not be sure of the patient’s WHO classification at the time of
the proteinuric flare. Nevertheless, because of the relatively
good coherence of the albuminuria–proteinuria relationships
among the individuals of this study, it seems unlikely that, at
least for the WHO classifications III, IV, and V, there are im-
portant differences in albuminuria–proteinuria relationships
according to WHO class.

This work does not determine whether the albuminuria–
proteinuria relationships differ between those tested during
SLE proteinuric flare compared with those tested during
chronic proteinuric states of SLE GN. To test that question
rigorously would require a testing protocol that was activated
in relationship to proteinuric flare; however, the protocol of this
study involved testing proteinuria at regular intervals, rather
than in response to proteinuric flare. Nevertheless, virtually all
of the data describing albuminuria–proteinuria relationships
under conditions of heavy proteinuria (e.g., P-C ratio >1.0)
represent SLE flare conditions. The reason is that virtually all of
the patients in the OSS who experienced proteinuric flare were
treated and achieved complete or near-complete remission of
their proteinuric flare. As a consequence, this study is largely
describing the albuminuria–proteinuria relationships under
conditions of SLE proteinuric flare.

This work shows that over the entire range of P-C ratios of
this study (0.0 to 6.5), A-C and P-C ratios are linearly related
and highly correlated. Specifically, albuminuria is nearly a
constant proportion of proteinuria over the range of P-C ratios
that define the low- (18,19), intermediate- (19,20), and high-
threshold criteria (22–26) for proteinuric flares. Thus, there
seems to be no advantage in measuring albuminuria rather
than proteinuria to diagnose SLE proteinuric flare; however,
measuring albuminuria might have an advantage in forecasting
SLE proteinuric flare. This is suggested by the finding that
albuminuria as a proportion of proteinuria (A-P ratio) rises
rapidly over the P-C range of 0.0 to 0.3. Thus, compared with
P-C ratio, monitoring trends in A-P ratio might be more sensi-
tive in identifying patients who have SLE GN and are at in-
creased risk for proteinuric flare. To test this hypothesis would
require study of a large cohort of patients who have SLE GN
and have developed complete remission (24-h urine P-C ratio
<0.3) and then are followed longitudinally for measurement of
both P-C and A-P ratios to determine which measure better
predicts renal flare. Although simple in concept, such a deter-
mination is well beyond the scope of this work.

The finding that the A-P ratio is more sensitive to changes in
low-level proteinuria than the P-C ratio, whereas the A-C ratio
is not, seems contradictory; however, comparing A-C with P-C
ratio (Figure 1) is a comparison of the absolute difference
between albuminuria and proteinuria. At normal proteinuria
rates (P-C ratios <0.3), the absolute differences between albu-
minuria and proteinuria are very small and for this reason are
not evident in Figure 1. By contrast, at P-C ratio <0.3, the
relative changes in albuminuria to proteinuria (A-P ratio) are
very large and therefore are evident when comparing A-P with
P-C ratio (Figure 2). Thus, for those with baseline low-level
proteinuria, monitoring change in A-P ratio should make it
easier to detect GN progression than measuring change in A-C
or P-C ratio.

Although A-P ratio is more sensitive to change than P-C ratio
when P-C ratio is in the normal range, we suggest that it cannot
be assumed that trends in A-P ratio would be more informative
than trends in P-C ratio in forecasting SLE flare. The basis for
this interpretation is that, in the OSS patients with GN and
low-level proteinuria, it is common to observe fluctuations in
the bimonthly 24-h urine P-C ratios (unpublished observa-
tions). These low-level fluctuations in 24-h P-C ratio could
represent subthreshold proteinuric flares that resolve sponta-
neously. Virtually all of the OSS patients were receiving predn-
isone, immunosuppressive therapy, or both. This therapy
could be sufficient to suppress a mild GN flare. Thus, having a
more sensitive method to detect “mini flares” (e.g., by monitor-
ing A-P ratio) might not be clinically important.

Consistent with the suggestion that spontaneous resolution
of mild SLE GN flares in those who are on maintenance therapy
are our previous observations (32). We found that patients who
had SLE GN and low-level proteinuria and experienced mild
nephritic flares (recurrence of red cell or mixed red cell leuko-
cyte casts) usually experienced remission without an increase in
immunosuppressive or steroid therapy (32). Furthermore, it is
plausible that the level of glomerular injury that carries a high
risk for progression to proteinuric flare is one that induces
nonselective proteinuria (both albumin and the larger molecu-
lar weight proteins are excreted in increased amounts in the
urine). Under that scenario, A-P ratio would have decreased
sensitivity to predict SLE flare because albuminuria and pro-
teinuria would change in parallel.

A further reservation regarding the routine use of microalbu-
minuria to monitor SLE GN status is the substantially greater cost of the microalbumin assay compared with the proteinuria assay (30). In light of all of these concerns, we suggest that monitoring SLE GN by routine microalbuminuria assay is not warranted at this time.

This study also shows that, in general, nonalbumin proteinuria (P-C ratio – A-C ratio) increases progressively with increasing P-C ratio. This is consistent with the notion that in SLE GN, the greater the P-C ratio, the greater is the amount of nonselective proteinuria. The rationale for using nonalbumin proteinuria as a surrogate for nonselective proteinuria is as follows: In patients with overt glomerulopathy, (1) increasing proteinuria is associated with increasing albuminuria (Figure 1). (2) As albuminuria increases, also increased is the excretion of both high molecular weight proteins (e.g., IgG, α2 macroglobulin, and IgM) and low molecular weight proteins (e.g., β2 microglobulin) (33–35). Thus, nonalbumin proteinuria (P-C ratio – A-C ratio) increases. Because the nonalbumin proteinuria fraction contains the high molecular weight proteins, it follows that increased nonalbumin proteinuria is evidence of increased nonselective proteinuria. Also, the pyrogallol method underestimates IgG by approximately one third (9). Thus, the increase in nonselective proteinuria suggested by Figure 3 is likely even greater than that shown by the term (P-C ratio – A-C ratio).

Nonselective proteinuria may be more nephrotoxic than selective proteinuria (30,31). Thus, the use of high-threshold criteria for SLE proteinuric flare (22–26) may expose the kidney to greater nephrotoxicity than the use of the low-threshold criteria for SLE flare (18–20). On this basis, it could be argued that, compared with the routine use of low-threshold criteria, the routine use of high-threshold criteria for proteinuric flare before triggering an increase in therapy will delay therapy and might increase the risk for irreversible kidney damage. Conversely, using the low-threshold criteria to trigger an increase in therapy might expose the patient to more steroid and immunosuppressive therapy than is needed to control SLE GN. No randomized trials have compared the risks and benefits of treating patients with SLE GN by the low-, medium-, or high-threshold criteria. Our data suggest, however, that this is an important issue that should be addressed in future studies.

Conclusions

For the diagnosis of proteinuria renal flare, measuring albuminuria offers no advantage over measuring total proteinuria because changes in P-C and A-C ratio are highly correlated over the designated ranges for SLE GN proteinuric flares; however, in those with normal-range proteinuria, subsequent changes in A-P ratio might be a better forecaster of renal flare than changes in P-C or A-C ratio. High P-C ratios are associated with evidence of nonselective proteinuria, which may increase the nephrotoxicity of proteinuria. Thus, using high-threshold criteria for SLE flare (allowing greater proteinuria increase before flare is declared) may expose the kidney to greater nephrotoxicity than using the low-threshold criteria for SLE flare.

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Disclosures

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