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Expert Review

Urine Protein Tests in Systemic Lupus Erythematosus: What Do They Mean?

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ABSTRACT. The development of lupus nephritis (LN) in patients with systemic lupus erythematosus is associated with increased morbidity and mortality. Proteinuria is a key indicator of kidney involvement; detecting and monitoring proteinuria is therefore crucial as it acts as a surrogate marker for disease activity and has significant prognostic value. This review explores the general mechanisms of proteinuria and highlights the limitations of current measurement techniques. In the absence of specific urinary markers for LN disease activity, evaluating proteinuria involves considering its trajectory, amplitude of change, and the overall clinical status of the patient. Differentiating between acute disease vs proteinuria that may stem from scarring and glomerular basement membrane remodeling can be challenging. Additionally, in the absence of other signs of active disease, the time to recovery and resolution of proteinuria may be prolonged.

Key Indexing Terms: albumin-to-creatinine ratio, lupus nephritis, protein-to-creatinine ratio, proteinuria, systemic lupus erythematosus

Introduction

Proteinuria is a major manifestation of lupus nephritis (LN). Guidelines around the diagnosis and management of LN often cite proteinuria and its measurement. In recent years, there have been new methods used to assess proteinuria, but these metrics are often not well understood. In this review, we will discuss how proteinuria develops anatomically, with an emphasis on glomerular vs tubular proteinuria, and the benefits and pitfalls of its measurement in the patient with systemic lupus erythematosus (SLE).

Pathophysiology of proteinuria

Proteinuria is one of the principal signs of kidney disease. Assessment of proteinuria is essential in diagnosing and monitoring the disease course. Additionally, it is a risk factor for progression to chronic kidney disease (CKD), owing to its proinflammatory and profibrotic effects on the kidneys.[1] Given its critical role, particularly in guiding treatment decisions for glomerular diseases such as LN, understanding the pathophysiology and limitations of detecting and quantifying proteinuria is important.

There are 2 general mechanisms identified in the abnormal excretion of urinary proteins (Figure 1A). The first mechanism involves changes that increase the permeability of the glomerular capillary wall, allowing albumin—which has an intermediate molecular weight (MW)—and high MW proteins to pass into the tubular lumen (Figure 1B). Under normal conditions, the glomerular ultrafiltrate typically contains proteins with MW < 60 kDa owing to the glomerular permselectivity.[2] Therefore, the composition of the protein in the ultrafiltrate can change depending on the type of renal disease and extent of injury. It is important to note that the glomerular capillary wall (filtration barrier) comprises 3 components: the fenestrated capillary endothelium; the basement membrane; and the visceral epithelium, also known as the podocyte. Podocyte injury leads to its detachment from the glomerular basement membrane, resulting in proteinuria.

The second mechanism involves the impairment of protein reabsorption at the proximal tubule. Under physiological conditions, low MW proteins and a very small fraction of albumin that pass through the glomerular filtration barrier are reabsorbed by tubular epithelial cells.[3] However, when there is an increase in protein filtration—whether as a result of damage to the glomerular filtration barrier or overproduction of protein (particularly low MW proteins, such as light chains in multiple myeloma)—protein reabsorption can be impaired, leading to protein loss in the urine.

The mechanism of filtered protein reabsorption is complex and involves receptors such as megalin and cubulin, which, when protein-bound, are internalized via endocytosis, resulting in protein degradation via lysosomes.[4] A defect in the receptors or overload of the receptor-binding sites can lead to inadequate absorption and excretion in the urine (Figure 1C). Additionally, low MW proteins could also exert direct toxic injury to tubular epithelial cells, especially in the context of overproduction due to plasma dyscrasias (Figure 1D).[5] Therefore, when there is an absorptive defect in the proximal tubules, the resultant escape of lower MW proteins in the urine is referred to as "tubular protein-

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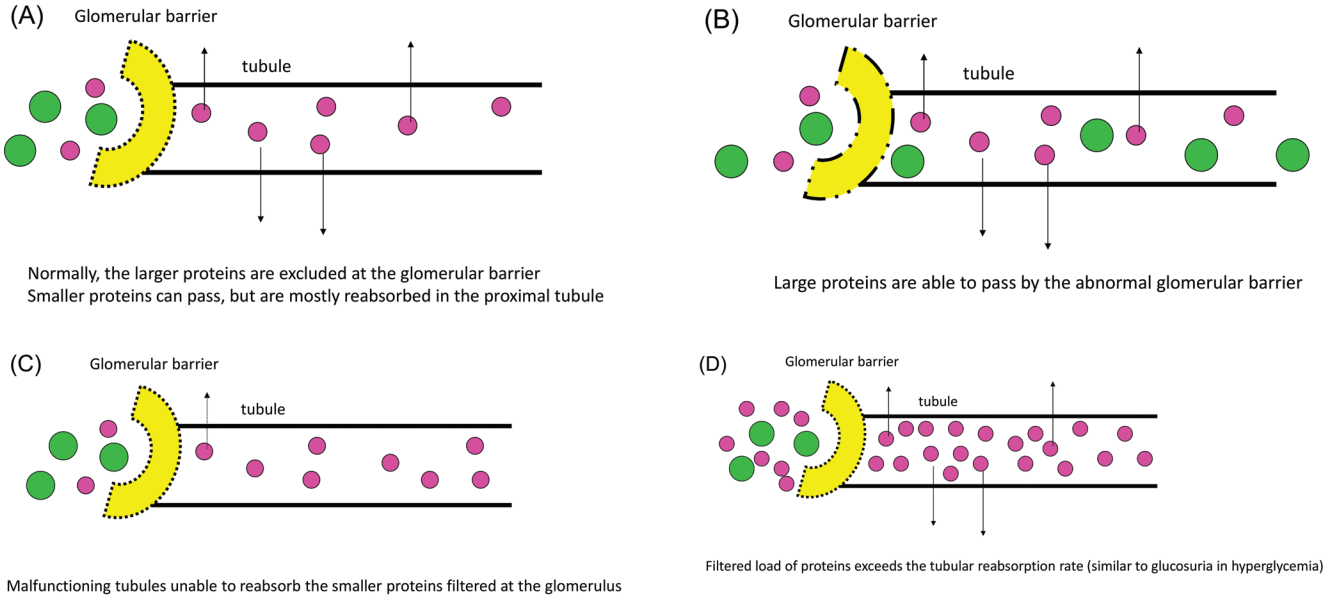

Figure 1. (A) General mechanisms of proteinuria: schematic representation of the glomerular barrier and renal tubular epithelial cells in the absence of clinically significant proteinuria. Under normal conditions, large proteins (high and intermediate MW), depicted in green, are unable to pass through the glomerular filtration barrier. Small proteins (mainly low MW), shown in pink, are filtered but then reabsorbed by the tubular epithelial cells. Therefore, minimal protein is excreted in the urine. (B) Glomerular proteinuria: under disease conditions that increase the permeability of the glomerular barrier, large proteins (such as albumin) leak through the glomerular barrier and are subsequently excreted in the urine. (C) Tubular proteinuria: small MW proteins (in pink) are not reabsorbed at the level of the tubular cells due to tubulointerstitial disease and are excreted in the urine. (D) Overflow proteinuria: filtered low MW proteins (in pink) overwhelm the absorption capacity of the proximal tubular cells and are therefore excreted in the urine. Examples include urinary light chains in multiple myeloma, and supranormal glomerular filtration rate, such as in pregnancy. In a normal pregnancy, the increased filtration load of protein secondary to physiologically increased GFR can lead to a mild increase in urinary protein excretion, typically remaining at < 300 mg/day. However, any proteinuria during pregnancy requires close monitoring and further investigation to rule out primary renal disease or the development of preeclampsia. GFR: glomerular filtration rate; MW: molecular weight.

uria" to distinguish it from that resulting from abnormalities in the glomerular filtration barrier.

In the early stages of glomerular injury, albumin (MW: 69 kDa) is the dominant protein excreted; however, with progressive damage, larger molecules such as IgG (MW: 150 kDa) are seen in the urine, and in very severe cases, higher MW proteins such as IgM (MW: 900 kDa) and α2-macroglobulin (MW: 720 kDa) reach the tubular lumen. It is postulated that these larger molecules may be a better marker for estimating the severity of the damage to the glomerular capillary wall (podocyte injury) than the overall amount of proteinuria.[3] Additionally, quantifying low MW proteins such as α1-microglobulin (MW: 31 kD) and β2-microglobulin (MW: 11.8 kD) can be helpful, as the presence of a large fraction in the urine would be a sign of escaped tubular reabsorption and is suggestive of tubulointerstitial injury. As an example of its usefulness, Bazzi et al[6] looked at the urinary excretion of IgG and α1-microglobulin in 78 patients with idiopathic membranous nephropathy. Based on their findings, IgG excretion was the most significant predictive marker of remission (100% vs 20% in patients with IgG excretion < 110 mg/g urine creatinine vs > 110 mg/g urine creatinine) and α1-microglobulin excretion predicted progression to renal failure. These findings suggest that low IgG excretion is indicative of reversible glomerular damage, whereas α1-microglobulin excretion is suggestive of tubulointerstitial damage, which is an important factor in progression to renal failure in almost all types of kidney disease.[6] Differential measurement of these urinary proteins is not currently used in clinical practice, although, as will be discussed, the urine protein-to-creatinine ratio (UPCR) vs the urine albumin-to-creatinine ratio (UACR) may be a way to examine glomerular vs tubular contribution to proteinuria.

Proteinuria that occurs as a result of urinary tract infections or inflammation of the urinary tract such as cystitis and urethritis, or as a result of hematuria (introduction of blood proteins) or urinary tract obstructions (eg, from tumor), are beyond the scope of this review.

Mechanism of proteinuria in LN. In LN, autoantibodies are formed against nuclear and cellular antigens. These immune complexes can be found in the mesangium along the glomerular basement membrane, subendothelial space, and subepithelial space, resulting in proteinuria. Complexes that are found in the subendothelial space injure endothelial cells and are characteristic of class III and IV LN. By accessing the vascular space, these deposits can attract circulating myeloid cells, leading to immune cell infiltration into the renal interstitium and triggering an inflammatory response. On the other hand, deposition of immune complexes in the subepithelial space can trigger podocyte injury through activation of the complement pathway[7]; this is classically seen in class V (membranous) LN.

The mechanisms of podocyte damage in LN are multifactorial, involving dysregulation of the actin cytoskeleton, apoptosis,

and impaired podocyte regeneration. These processes contribute to persistent proteinuria, glomerular scarring, and progression to CKD.[8] Notably, proteinuria itself can further hinder podocyte regeneration.[9] Additionally, complement components in the urine can damage tubular epithelial cells and result in progressive interstitial disease.[10] Similarly, inability to regenerate injured tubular epithelial cells can lead to tubular atrophy and loss of nephron mass.[11] Given the above findings, proteinuria is routinely assessed in clinical practice as a marker of disease activity and damage in LN.

- *Proteinuria definition and measurement.* Under normal conditions, < 150 mg of total protein is excreted in the urine per day. The normal rate of albumin excretion as per the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines is < 30 mg/day[12]; however, the normal range may be considered as low as 20 mg/day.[13] In healthy young adults, it is closer to 4-6 mg/day.[14]

Currently, there are 2 methods to detect proteinuria. Semiquantitative measurement can be performed using a standard urine dipstick and sulfosalicylic acid (SSA) test. Quantitative measurements include 24-hour urine collection and spot urine tests, such as UPCR and UACR.

- *Urine dipstick.* This method is specifically used to detect urinary albumin. However, the detection limit of urine albumin concentration is 10-20 mg/dL. Therefore, it is specific but not sensitive in detecting low levels of urinary albumin. There are a few drawbacks to using urinary dipstick, as it is affected by urinary concentration. For example, mildly increased albuminuria in a patient may not be detected unless the urine is concentrated. False positives can also occur if the urine is highly alkaline or was measured within 24 hours of iodinated contrast exposure or in the presence of gross hematuria. Although this test is usually used as an initial screening test, it has a high degree of variability in detecting proteinuria. Additionally, the results poorly correlate with a quantitative 24-hour urine protein measurement.[15] Therefore, a quantified proteinuria assay is considered a more accurate screening tool for diagnostic evaluation, especially in LN.[16] A recent study investigated the use of urine specific gravity (SG) to improve the accuracy of detecting significant proteinuria with urinary dipsticks.[17] According to the findings, significant proteinuria was identified when the SG was ≤ 1.0012 for a trace amount, 1.0237 for 30 mg/dL, and 1.0442 for 100 mg/dL of protein on the dipstick (normal urine SG varies between 1.005 and 1.030). The study also noted that the likelihood of significant proteinuria was very high if the dipstick indicated ≥ 300 mg/dL of protein at any SG.[17]

- *SSA test.* In contrast to the urine dipstick test, the SSA test detects all proteins, not just albumin, at a sensitivity of 5-10 mg/dL. It is generally used when there is a suspicion of urinary immunoglobulin light chains (Bence-Jones proteins; see Figure 1D). This test can also be falsely positive after exposure to iodinated contrast or if the urine contains penicillin or cephalosporins or its derivatives.

- *24-hour urine collection.* The gold standard for measurement of protein excretion is a 24-hour urine collection, as it is less subject to variation as a result of changes in protein excretion from physical activity, circadian rhythm, posture, and hydration status. However, this test is cumbersome for most patients and is susceptible to errors such as undercollection (< 24 hours) and overcollection (> 24 hours). In order to assess the accuracy of a 24-hour collection, total urine creatinine (mass/day) is measured and is compared to an expected creatinine excretion, which is 20-25 mg/kg of lean body weight in male individuals and 15-20 mg/kg in female individuals.[18] Urine volume should not be used as a measure of completeness of the collection, as it will vary with the hydration status of the patient. The production and secretion of creatinine itself is also subject to variation. Even newer equations, which take into account age, sex, and weight, still do not adjust for variation in creatinine production. Additionally, in chronic disease states, there has been an association between decreased urinary creatinine excretion and increased mortality, presumably because of lower muscle mass.[19,20] This issue is especially important in high catabolic states such as nephrotic syndrome,[21] in which urine creatinine excretion can be unreliable. Treatment with glucocorticoids is known to reduce creatinine generation through drug-induced muscle catabolism (sarcopenia),[22] which can also affect the interpretation of a 24-hour urine protein collection. Therefore, 24-hour urinary measurements should be analyzed with caution and should always take into consideration the patient's overall clinical picture. In the same patient, 24-hour urine proteins should only be compared if the total 24-hour urine creatinine is similar.

- *UPCR.* Spot urine collection was first proposed by Ginsberg et al in 1983[23] to simplify the method of urinary protein estimation. This method assesses the UPCR in a single voided urine sample and was mainly designed to differentiate between nephrotic and nonnephrotic range proteinuria.[24] However, this approach relies on the assumption that the excretion of protein and creatinine remains stable throughout the day. Therefore, spot urinary tests provide only a snapshot of the day. Interestingly, dilute urine, as evidenced by low SG, was shown to overestimate protein excretion. In contrast, UPCR of concentrated urine was more likely to result in an underestimation of protein excretion compared to an adequately collected 24-hour urine sample.[25] In countries using the International System of Units (SI), the result is usually reported as "mg protein/mmol creatinine." As an example, a result such as 80 mg/mmol creatinine could be extrapolated to an estimated 24-hour urine excretion of 10 mmol creatinine, so that the estimated 24-hour excretion of protein would be 80 mg/mmol creatinine × 10 mmol creatinine in 24 hours = 800 mg protein in 24 hours. In the United States, it is shorthand to use an "average" 24-hour urine creatinine excretion of 1 g/day, so that proteinuria is usually expressed as *X* g/g (creatinine) and is assumed to approximate what would be excreted in 24 hours. Additionally, there are other conventional units used to report proteinuria that adopt a similar assumption of an average daily creatinine excretion of 1 g creatinine/day. For example, a urine protein concentration of 30 mg/mg would be equivalent to 0.03 g/day, and a proteinuria of 3 g/g would be approximately 3 g/day of protein excretion in the urine. It is important to note that daily creatinine excre-

tion varies based on age, sex, body weight, and body mass.[26] The 1 g/day (8.84 mmol/day) value used here is an average estimate commonly applied in clinical practice to simplify calculations for total 24-hour measurements.

- *24-hour UPCR vs 24-hour urine protein measurement (used in clinical trials).* Given the limitations of spot UPCRs—namely, their potential for high variability—an alternative approach has been devised that estimates 24-hour urine protein from the UPCR of a 24-hour urine collection. The rationale behind this method is that as the collection duration approaches 24 hours, the resulting UPCR more accurately represents that of a full 24-hour urine collection.[27] Additionally, 24-hour UPCR corrects for undercollection and overcollection, whereas adjustment with 24-hour creatinine is often not applied to the 24-hour collection. Interestingly, in the data collected from the Modification of Diet in Renal Disease (MDRD) cohort, 24-hour UPCR was shown to be a better predictor of glomerular filtration rate (GFR) decline as compared to the 24-hour urine protein collection.[28] This approach of using 24-hour UPCR has been used as an endpoint in clinical trials. Alternatives, such as using the first morning void, are less accurate. Although the first morning void reflects an overnight collection, it underestimates UPCR by 20%. Its short duration is also influenced by factors such as diet, nocturia, and sleep quality and therefore would not be suitable for a clinical trial. Notably, a study by Koopman et al showed that even under controlled conditions, sequential 3-hour urine samples had highly variable UPCR values.[29] Therefore, it is recommended that collected urine samples represent a substantial portion—at least 50%—of a complete 24-hour collection based on creatinine content, to provide a UPCR that closely approximates a 24-hour UPCR.[30] In other words, a longer collection provides a UPCR that reflects the integrated mean of UPCRs over the entire collection period.[31]
- *UACR.* Measurement of urinary albumin excretion has become a marker for renal and cardiovascular disease (CVD) as a reflection of vascular damage and is especially used in conditions such as diabetic or hypertensive nephropathy. An albumin excretion > 30 mg/day is associated with an increased risk of CVD,[32,33] and KDIGO guidelines emphasize monitoring albuminuria, as it is a significant predictor of CKD progression. However, the albumin excretion rate is not commonly used in nondiabetic forms of glomerular disease, and the relationship between albuminuria and proteinuria has not been examined in SLE. Additionally, measuring nonalbumin proteinuria may indicate higher tubular toxicity and could be more indicative of tubulointerstitial inflammation, especially in LN.[34,35]

Albumin excretion, similar to total protein, varies throughout the day, posing similar challenges in measurement reliability. However, there is an advantage to its use as it is considered more sensitive and more specific—though more expensive—for the detection of proteinuria, especially at its early stages.[36] A first morning void best correlates with a 24-hour urine albumin collection,[36,37] although it has limitations, as discussed above. Another important consideration is the lack of standardization of urine albumin assays. Efforts to standardize these tests are ongoing, but challenges remain owing to the immunometric nature of these tests. A standardized reference system is crucial for ensuring the accuracy and comparability of urine albumin measurements across different laboratories and methods.

Proteinuria assessment in patients with LN

Among patients with SLE, the life-time incidence of LN is roughly 20% to 60%. LN confers a greater risk of morbidity and mortality and approximately 10% to 30% will progress to kidney failure, requiring renal replacement therapy. Therefore, assessing and monitoring proteinuria, a marker of disease activity, is of utmost importance. Table 1 summarizes the diagnostic criteria of LN based on guidelines provided by KDIGO, the American College of Rheumatology, and the European Alliance of Associations for Rheumatology (EULAR). KDIGO guidelines recommend initial testing with spot UPCR and urinary dipstick. Thereafter, results should be quantified by a 24-hour urine protein test. Random UACR and UPCR are discouraged owing to the limitations discussed in previous sections and, if used, are recommended to be taken at the same time of day and under similar conditions, which is often not feasible.

There have been conflicting data regarding the correlation between UPCR and 24-hour urine protein. This has been most extensively studied in SLE and a summary of the results from selected studies are found in Table 2. A systematic review by Medina-Rosas et al examined 13 studies involving patients with LN and highlighted several shortcomings.[38] These included inadequate/small sample sizes, insufficient information on LN disease activity and the phase of therapy, and the use of correlation analysis instead of agreement analysis in the statistical methods. Consequently, the UPCR was found to be an inadequate measure of 24-hour urine protein and was not recommended as a substitute for a 24-hour urine protein collection.[38,39] In a prospective cohort of 75 patients with LN (TUNARI study[40]), UPCR and 24-hour urine protein were correlated; however, the precision of the test decreased with higher degrees of proteinuria and was more reliable at low levels (< 0.78 g/day). Interestingly, UPCR was also dependent on renal function and lost its discriminatory capacity as a triage test with a GFR < 30 mL/min. Leung et al[41] showed reasonable agreement between UPCR and 24-hour protein within a proteinuria range of 0.5-2 g/day, but the agreement decreased with higher levels of proteinuria. Guedes Marques et al[42] showed poor correlation with proteinuria < 500 mg/day and no correlation with proteinuria 500-1000 mg/day, which is quite concerning, as this would be the range seen in patients in remission in whom detecting an early flare would be essential. At this stage, it appears that UPCR cannot reliably predict 24-hour urine protein in LN, and this issue is much more pronounced in patients with SLE than would be expected in the general population with CKD.[43] However, in other glomerular diseases such as IgA nephropathy, UACR and UPCR correlate with 24-hour urine protein[44]; UACR performed best, predicting a decline in GFR by 50%.[45] A good correlation between UACR and 24-hour urine protein was also seen in amyloid light chain (AL) amyloidosis (Table 2).[46,47]

Therefore, when making decisions regarding monitoring

Table 1. Proteinuria measurement in LN based on various guidelines.

Guidelines	Diagnosis Criteria of LN	Proteinuria Target	
		Complete Response	Partial Response
KDIGO 2024	Testing panel: Urine dipstick > 2+ (any specific gravity), dipstick protein > 1+ (low specific gravity), or spot UPCR > 500 mg/g. Urine sediment positive for acanthocytes (≥ 5%), RBC casts, or WBC casts Quantify proteinuria: 24-h UP > 0.5 g/d Favor 24-h UP measurement in glomerular disease	Reduction in proteinuria < 0.5 g/g (50 mg/mmol) measured as the UPCR from a 24-h urine collection Stabilization or improvement in kidney function (± 10-15% of baseline) within 6-12 mos of starting therapy	Reduction in proteinuria by ≥ 50% and to < 3 g/g (300 mg/mmol) measured as the UPCR from a 24-h urine collection Stabilization or improvement in kidney function (± 10-15% of baseline) within 6-12 mos of starting therapy
ACR 2012	Persistent proteinuria > 0.5 g/day or > 3+ by dipstick, and/or cellular casts including RBC, hemoglobin, granular, tubular or mixed A spot UPCR > 0.5 can be substituted for the 24-h UP measurement, and active urinary sediment (> 5 RBC/HPF, > 5 WBC/HPF in the absence of infection, or cellular casts limited to RBC or WBC casts) can be substituted for cellular casts.	UPCR < 0.2 g/g; eGFR at baseline or improvement by 25%; inactive urinary sediment	50% reduction in UPCR and UPCR 0.2-2 g/g; eGFR at baseline level or improvement by 25%; inactive urinary sediment
EULAR 2019	24-h UP > 0.5 g/d or equivalent spot UPCR	UPCR < 0.5 g/g (< 50 mg/mmol); serum creatinine within 10% of previous baseline	≥ 50% reduction in UPCR, to subnephrotic range and serum creatinine within 10% of prior baseline by 12 mos of treatment

ACR: American College of Rheumatology; eGFR: estimated glomerular filtration rate; EULAR: European Alliance of Associations for Rheumatology; HPF: high-power field; KDIGO: Kidney Disease: Improving Global Outcomes; LN: lupus nephritis; RBC: red blood cell; UP: urine protein; UPCR: urine protein-to-creatinine ratio; WBC: white blood cell.

and management of proteinuria in LN, UPCR can be used as a screening test. However, this should be complemented by an accurate 24-hour urine collection. The patient should receive instructions on how to properly carry out a 24-hour collection, including discarding the first morning void on day 1 and saving the first morning void on day 2. Additionally, any decision regarding a change in treatment plan must also consider the trajectory of the change in proteinuria, as persistent proteinuria maybe be a result of scarring and reflective of chronic damage and would not necessarily indicate active disease. Other factors to consider include SLE serological markers (C3, C4, dsDNA), serum albumin, and the overall clinical picture, as 24-hour proteinuria measurements are also subject to errors, even after ensuring an adequate collection by correcting for the urine creatinine. An interesting observation was made in the Nephrotic Syndrome Study Network (NEPTUNE) cohort (SLE-excluded) of patients with biopsy-proven glomerulonephritis. In this cohort, urine creatinine excretion was less than expected, which was attributed to high catabolic state and glucocorticoid use.[48] Therefore, since gold standards for predicting creatinine excretion are lacking and other urinary markers are currently unavailable, all changes in urinary protein must be analyzed with caution. Additionally, changes in proteinuria, such as a change in UPCR from 80 mg/mmol to 90 mg/mmol, should not be considered clinically significant as this could be attributed to random variation. Therefore, as discussed earlier, it is crucial to assess the entire clinical context when determining treatment strategies for managing patients with LN.

Proteinuria and progression to endstage renal disease. There are several factors associated with progression of LN to endstage kidney disease (ESRD). These include impaired kidney function at the time of diagnosis, nephrotic-range proteinuria, and poor response or nonadherence to immunosuppressive treatment. Persistent proteinuria increases the risk of progression to ESRD and predisposes a patient to CKD. Many studies have looked at the long-term renal outcomes in complete or partial remission of proteinuria. Data from the MAINTAIN Nephritis Trial showed that achieving a proteinuria level of < 0.7 g/day after 12 months of treatment was a marker of good renal outcome.[49,50] Similarly, data from the Euro-Lupus Nephritis Trial demonstrated that a proteinuria value < 0.8 g/day at 12 months was the best predictor of long-term outcomes in patients with LN. Sustained proteinuria > 2 g/day was associated with an almost 7-fold greater rate of renal functional decline (–6.68 mL/min/1.73 m^2/year) in a cohort of patients with SLE.[51] Nephrotic-range proteinuria in a case-control study of 213 patients with SLE, along with elevated creatinine at the time of kidney biopsy and higher chronicity index on renal biopsy, was also associated with poor outcomes.[52] This is likely reflective of irreversible histological damage and chronic scarring.

When monitoring proteinuria, it is also important to consider that the time to resolution of proteinuria or a clinically meaningful response can be in the order of years. Of note, complete remission, defined as proteinuria of < 0.5 g/day, was achieved in 72% of patients in 2 years in a study by Medina-Rosas et al,[53] and achieved in 52% of patients within 2 years and

Table 2. Correlation among UACR, UPCR, and 24-h UP.

Study First Author and Date	Study Focus	UP Measures	Correlation
Yu 2022[45]	IgA nephropathy	UACR, UPCR, 24-h UP	UACR, UPCR, and 24-h UP showed high correlation. In univariate analysis, UACR performed better in predicting the prognosis of IgA nephropathy.
Huan 2016[44]	IgA nephropathy	UACR, 24-h UP	Good correlation between UACR and 24-h UP except in CKD stage 5.
Visram 2020[46]	AL amyloidosis	UACR, 24-h UP	Strong correlation between UACR and 24-h UP.
Mendelson 2022[47]	AL amyloidosis	UPCR, 24-h UP	Moderate correlation between UPCR and 24-h UP.
Gutiérrez-Peredo 2023 (TUNARI study)[40]	LN	UPCR, 24-h UP	UPCR showed high sensitivity to follow-up patients with LN as compared with 24-h protein. UPCR (untimed) was useful in patients in complete remission (< 0.3 g/d); however, utility was limited in partial remission.
Hogan 2016 (NEPTUNE cohort)[48]	Glomerular disease	UPCR, 24-h UP	Random UPCR was only modestly correlated with 24-h UP
Medina-Rosas 2016 (SR and metaanalysis)[38]	LN	UPCR, PCR, 24-h UP	UPCR has utility as a screening test, but there was poor agreement between UPCR and 24-h UP.
Medina-Rosas 2015[39]	LN	Untimed UPCR, 24-h UP	UPCR to be used as a screening test only and results need to be validated with 24-h UP.
Guedes Marques 2013[42]	LN	Random UPCR, 24-h UP	Correlation was poor with proteinuria < 500 mg/d and there was no correlation with proteinuria between 500-1000 mg/d.
Birmingham 2008[35]	LN	UACR, UPCR, 24-h UP	Measuring albuminuria offered no advantage over measuring total proteinuria because changes in UACR and UPCR are correlated.
Leung 2007[41]	LN	Untimed UPCR, 24-h UP	Good correlation and limited agreement between UPCR and 24-h UP. Use UPCR in screening and monitoring for proteinuria.

AL: amyloid light chain; CKD: chronic kidney disease; LN: lupus nephritis; NEPTUNE: Nephrotic Syndrome Study Network; SR: systematic review; UACR: urine albumin-to-creatinine ratio; UPCR: urine protein-to-creatinine ratio; UP: urine protein.

74% only after 5 years in a study by Touma et al.[54] Both studies highlight the importance of time in the repair and/or healing of the glomerular barrier. In a large Italian cohort of patients with LN (303 patients), Gatto et al found that approximately 84.8% of the patients achieved complete remission after 1.44 years (median follow-up 0.69-3.58 years) following the initiation of treatment. Similar to the previous studies highlighted above, the probability of achieving sustained complete remission increased with time and was 40% at 1 year as compared to 90% at 15 years.[55] These observations suggest that it may not be appropriate to escalate immunosuppression solely because of slow resolution of proteinuria.[56]

Proteinuria from LN differs from residual proteinuria, which arises from the remodeling of the glomerular basement membrane, loss of podocytes, and/or tubular dysfunction, along with a limited capacity to regenerate tubular epithelial cells. It is crucial to make this distinction because, again, increasing immunosuppressive therapy in such cases would not be advantageous and could potentially lead to more harm due to side effects.

It is interesting to note that even with the resolution of proteinuria, a subset of patients with LN can continue to have deterioration in kidney function. In a single-center study of patients with the first episode of biopsy-proven LN, it was shown that despite resolution of proteinuria at 1 year, 33% of the complete responders continued to accrue renal damage (estimated GFR decline: −5 mL/min/1.73 m^2/year).[57] In a retrospective study of 151 patients with SLE and low-grade proteinuria, Wang et al showed that 50% progressed to a UPCR of > 0.5 g/g over a span of 1.2 years. This progression was correlated with low serum complement levels and shorter duration of SLE. Other associated factors included concomitant hypertension, diabetes mellitus, younger age, and the presence of hematuria.[59] Low complement levels had a high sensitivity (82%) and a negative predictive value of 92% for progression to overt proteinuria in their study.[58] Overall, this is likely indicative of a more active disease as suggested by the low serum complement levels, which is likely reflective of an ongoing inflammatory response. At this stage, owing to the absence of urinary or plasma biomarkers of disease activity, an ongoing challenge remains in distinguishing between active vs chronic SLE activity. Proteinuria stands as the current primary method for monitoring LN. However, given its limitations in measurement and variability, it should not be used in isolation. UPCR and 24-hour urine protein should be analyzed with caution when choosing to adjust immunosuppressive therapy.

Conclusion

In summary, LN is associated with a significant increase in morbidity and mortality. Measurement of proteinuria is crucial

for monitoring disease activity; however, the techniques for its measurement have limitations. Although the goal is to achieve complete remission, treatment decisions should not rely solely on single proteinuria measurements. Instead, they should consider the trajectory of change in proteinuria and other serological markers (eg, serum complements, serum albumin, dsDNA), and acknowledge potential delays in response to resolution of proteinuria, as well as the possibility of persistence as a result of chronic scarring.

CONTRIBUTIONS

MA: preparation and creation of the original draft; JB: critical review and editing of the manuscript.

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