

Proteinuria in Immune-Mediated Glomerular Diseases as a Marker of Disease Activity and Therapeutic Response: A Retrospective Study

Miroslava Stancheva Benkova-Petrova^{1,2}, Simona Bogdanova-Petrova^{1,3*}

1. Medical University “Prof. Dr. Paraskev Stoyanov”, Varna, Bulgaria

2. Clinic of Nephrology, St. Marina University Hospital, Varna, Bulgaria

3. Clinic of Rheumatology, St. Marina University Hospital, Varna, Bulgaria

* Correspondence:

Simona Bogdanova-Petrova

Medical University “Prof. Dr. Paraskev Stoyanov”, Varna, Bulgaria

Email: simona_bogdanova@yahoo.com

ORCID: 0000-0002-2601-2021

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Abstract

Background: Proteinuria is an established marker of activity, severity, and progression in glomerular diseases. In addition to reflecting damage to the glomerular filtration barrier, it also plays a pathogenetic role in the development of tubulointerstitial inflammation and fibrosis. **Objectives:** To assess the dynamics of proteinuria in patients with chronic glomerulonephritis and its significance as an indicator of therapeutic response. **Methods:** A retrospective study of a total of 57 patients with different morphological forms of chronic glomerulonephritis, treated at the Clinic of Nephrology and Dialysis, St. Marina University Hospital – Varna, were followed for a period of 24 months. Twenty-four-hour proteinuria and the protein-to-creatinine ratio (Pr/Cr) in a spot urine sample were analyzed. All patients received optimal nephroprotective therapy, and immunosuppressive treatment was administered when indicated. **Results:** The mean baseline 24-hour proteinuria was 5.94 g/24 h. By the third month, a statistically significant decrease to 3.65 g/24 h was observed ($p \approx 0.008$), followed by a further reduction to 2.7 g/24 h at month 6 and to 1.72 g/24 h at month 12. The observed reduction indicates an early and sustained therapeutic response in the studied patient population. Analysis

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of the protein-to-creatinine ratio confirmed the same favorable trend and supports its applicability as a reliable marker for monitoring proteinuria in clinical practice. **Conclusion:** Early and sustained reduction of proteinuria is a reliable indicator of therapeutic efficacy in chronic glomerular diseases and is associated with a more favorable renal prognosis. Proteinuria has substantial value both as a prognostic marker and as a surrogate endpoint in clinical follow-up.

Keywords: proteinuria; chronic glomerulonephritis; chronic kidney disease; therapeutic response

1. Introduction

Proteinuria is one of the most common and clinically significant manifestations of glomerular diseases. An increased urinary protein excretion not only reflects damage to the glomerular filtration barrier but also has major implications for long-term renal prognosis [1,2]. In recent years, growing attention has been paid to proteinuria as a modifiable risk factor for progression of chronic kidney disease (CKD).

Accumulated clinical data indicate that the degree of proteinuria is directly associated with the rate of decline in renal function. Patients with persistent proteinuria have a substantially higher risk of developing chronic renal failure [3]. For this reason, reduction of proteinuria is considered an important therapeutic goal and is frequently used as a surrogate marker of treatment efficacy in glomerular diseases [4].

The glomerular filtration barrier consists of endothelial cells, the glomerular basement membrane, and podocytes, which together provide selective filtration of plasma components. In glomerular diseases, structural and functional disturbances of this barrier lead to increased permeability to proteins, predominantly albumin [5].

Filtered proteins reach the proximal tubules where they are reabsorbed via endocytosis. When the amount of filtered protein exceeds the reabsorptive capacity of tubular cells, a series of pathophysiological mechanisms are activated, including inflammatory processes, oxidative stress, and release of profibrotic mediators [6,7]. As a result, tubulointerstitial changes develop that play a central role in progression of CKD.

Several studies demonstrate that even moderate levels of proteinuria may be associated with accelerated loss of renal function. Reduction of proteinuria has been associated with slowing of renal injury progression and improved long-term prognosis [3,7].

Importantly, a substantial proportion of glomerular diseases arise in the context of systemic rheumatologic disorders. Conditions such as systemic lupus erythematosus, ANCA-associated vasculitis, cryoglobulinemic vasculitis and secondary amyloidosis represent key examples in which renal involvement significantly determines overall prognosis. In these settings, proteinuria is not only a marker of renal injury, but also reflects systemic disease activity and therapeutic response. Therefore, evaluating proteinuria as a dynamic and modifiable parameter has direct implications for both nephrology and rheumatology practice.

Conventional endpoints in nephrology clinical trials, such as doubling of serum creatinine or progression to end-stage renal disease, require prolonged follow-up. Therefore, earlier indicators that reflect therapeutic effects on renal function are sought [2,8].

In this context, reduction of proteinuria is accepted as a reliable indicator of favorable renal outcome. Multiple studies show that early decrease in proteinuria after initiation of therapy is associated with a significantly lower risk of CKD progression [8,9]. Achieving proteinuria values below 1 g/24 h is often linked to better renal prognosis across various glomerular diseases [9,10].

ACE inhibitors and angiotensin receptor blockers are a cornerstone of treatment for renal diseases. By reducing intraglomerular pressure, these agents limit protein filtration and produce substantial reductions in proteinuria [11,12].

Moreover, RAAS blockade confers additional nephroprotective effects, including anti-inflammatory and antifibrotic actions [7,11]. There is compelling evidence that long-term therapy with these agents can slow progression of chronic kidney disease [11,12].

SGLT2 inhibitors represent a relatively new class of agents with nephroprotective properties. Their actions include restoration of tubuloglomerular feedback and reduction of glomerular hyperfiltration, resulting in decreased intraglomerular pressure [13,14].

Accumulating evidence indicates that treatment with SGLT2 inhibitors leads to significant reductions in albuminuria and delays progression of CKD in patients with various nephropathies [13,14].

Endothelin-1 participates in the pathogenesis of glomerular diseases by promoting vasoconstriction, inflammation, and fibrosis. Activation of the endothelin system may contribute to podocyte injury and increased proteinuria [15].

Endothelin receptor antagonists have shown promising results in reducing proteinuria in patients with glomerular diseases. Their effects include improvement of glomerular hemodynamics and attenuation of inflammatory processes [15,16].

In immune-mediated glomerular diseases, immunosuppressive therapy plays a key role in disease control. By suppressing the immunologic mechanisms of glomerular injury, these agents can produce marked reductions in proteinuria [1,17].

Achievement of partial or complete remission of proteinuria after immunosuppressive treatment is associated with a more favorable renal prognosis in diseases such as membranous nephropathy, IgA nephropathy, and lupus nephritis [10,17].

2. Materials and Methods

We present the results of a 2-year retrospective, single-center follow-up study including 57 patients from the Clinic of Nephrology and Dialysis at St. Marina University Hospital, Varna. All participants had morphologically verified chronic glomerulopathies and were clinically followed and evaluated using routine diagnostic methods. The analysis of available data includes participants with various morphological forms of immune-mediated glomerular diseases, including IgA nephropathy, membranous nephropathy, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, minimal change disease, lupus nephritis, and ANCA-associated glomerulonephritis. The exclusion criteria were: (1) age under 18 years; (2) patients with established malignant diseases; (3) pregnancy; (4) status post kidney transplantation; and (5) patients with incomplete laboratory or medical data. Given the retrospective design, informed consent was not required. All data were anonymized prior to analysis.

Descriptive statistics were applied for baseline characteristics. Changes over time were assessed using paired tests, while between-group

differences were analyzed using one-way ANOVA. A p-value <0.05 was considered statistically significant.

Patients were followed for 24 months; 24-hour proteinuria and the protein/creatinine ratio (Pr/Cr) in spot urine samples were analyzed.

All patients received optimal supportive therapy, including RAAS blockade (ACE inhibitors or ARBs), statins, diuretics, and other nephroprotective medications. Immunosuppressive treatment was administered where indicated, tailored to the type and severity of the glomerular disease, and included corticosteroids (parenteral and oral), cyclophosphamide, mycophenolate mofetil (MMF), azathioprine, and calcineurin inhibitors (tacrolimus). In some patients, an SGLT2 inhibitor (dapagliflozin) was added to the therapeutic regimen.

3. Results

The gender distribution of participants was 25 women and 32 men, or 43.86% : 56.14% (Table 1).

Table. 1. Distribution of patients by gender.

Gender	Number	Distribution %
F	25	43.86
M	32	56.14

The average age of all patients with HGN at the time of inclusion in the follow-up is 48.5 years (participants are aged between 19 and 78) (Table 2, Figure 1).

Table. 2. Statistical characteristics of patient age.

	Average value	Minimal	Maximal	Standard deviation.
Age	48.5	19	78	14.9

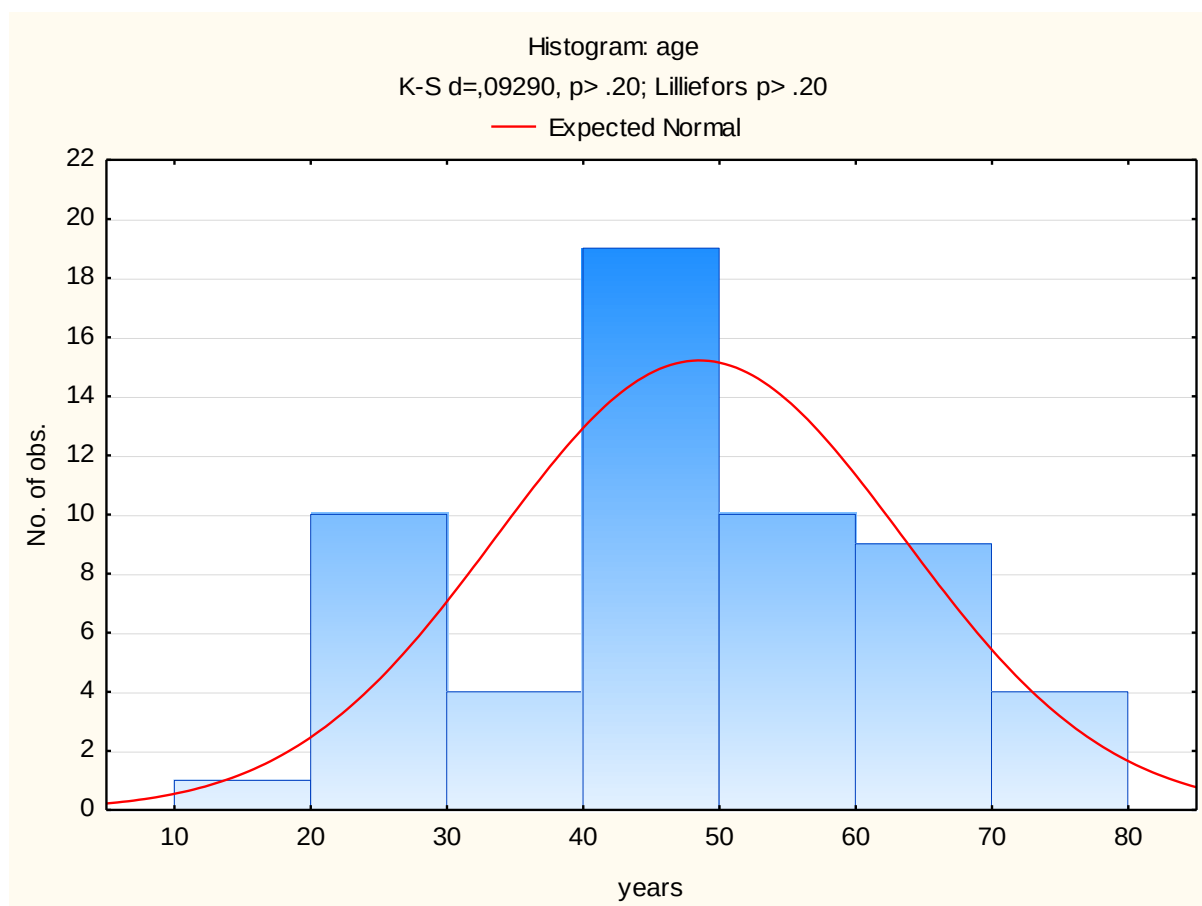


Figure 1. Histogram illustrating the number of participants in the follow-up according to age.

At baseline the mean 24-hour proteinuria among enrolled patients was approximately 5.94 g/24 h, corresponding to the nephrotic range and reflecting a substantial degree of glomerular injury. During treatment a marked reduction in this parameter was observed. By month 3 the mean proteinuria declined to about 3.65 g/24 h ($p \approx 0.008$). The reduction of roughly 2.3 g/24 h is clinically meaningful and demonstrates early therapeutic efficacy. Such a decrease is important because it is associated with stabilization of glomerular function and a reduced risk of progressive renal injury.

By month 6 proteinuria fell further to approximately 2.7 g/24 h. Although the difference versus month 3 did not reach statistical significance ($p \approx 0.148$), the downward trend remained evident. This suggests a sustained therapeutic effect of the interventions, likely reflecting both hemodynamic effects of nephroprotective therapy and gradual suppression of immunologic activity in patients who received immunosuppression.

At 12 months the mean 24-hour proteinuria declined to about 1.72 g/24 h. This value indicates that a substantial proportion of patients achieved partial or complete laboratory remission. Attainment of such levels is an important therapeutic milestone, being associated with markedly better renal prognosis and a lower risk of progression to chronic renal failure (Figure 2).

Additional analysis of the protein/creatinine ratio (Pr/Cr) in spot urine samples confirmed the trend observed with 24-hour proteinuria. Pr/Cr is widely used in clinical practice as a convenient and reliable surrogate for total proteinuria because it correlates with 24-hour collections, although careful interpretation is required at higher proteinuria levels. In the present analysis Pr/Cr values showed a statistically significant reduction at months 3 and 6, consistent with the decreases in 24-hour proteinuria.

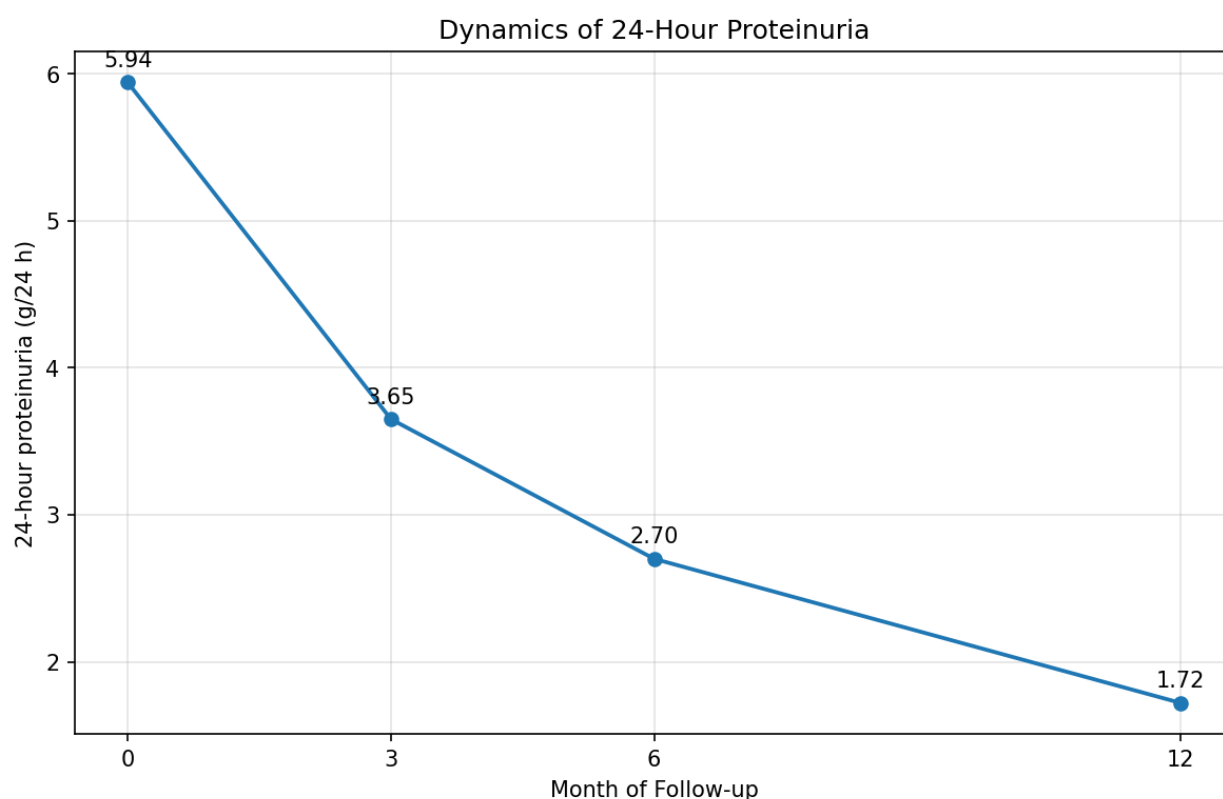


Figure 2. Dynamics of 24-hour proteinuria during follow-up.

One-way analysis of variance (ANOVA) was performed to compare mean protein-to-creatinine ratio (Pr/Cr) at baseline and at month 24 across the study groups (Figure 3 and Figure 4).

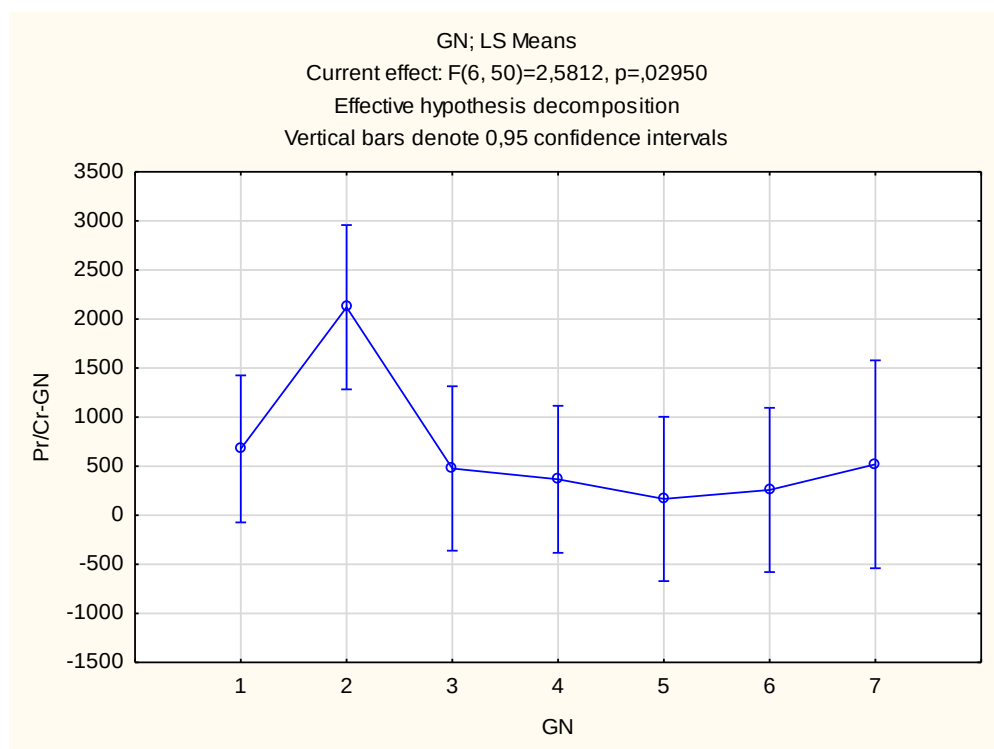


Figure 3. Analysis of variance (ANOVA) assessing differences in mean protein-to-creatinine ratio (Pr/Cr) at baseline.

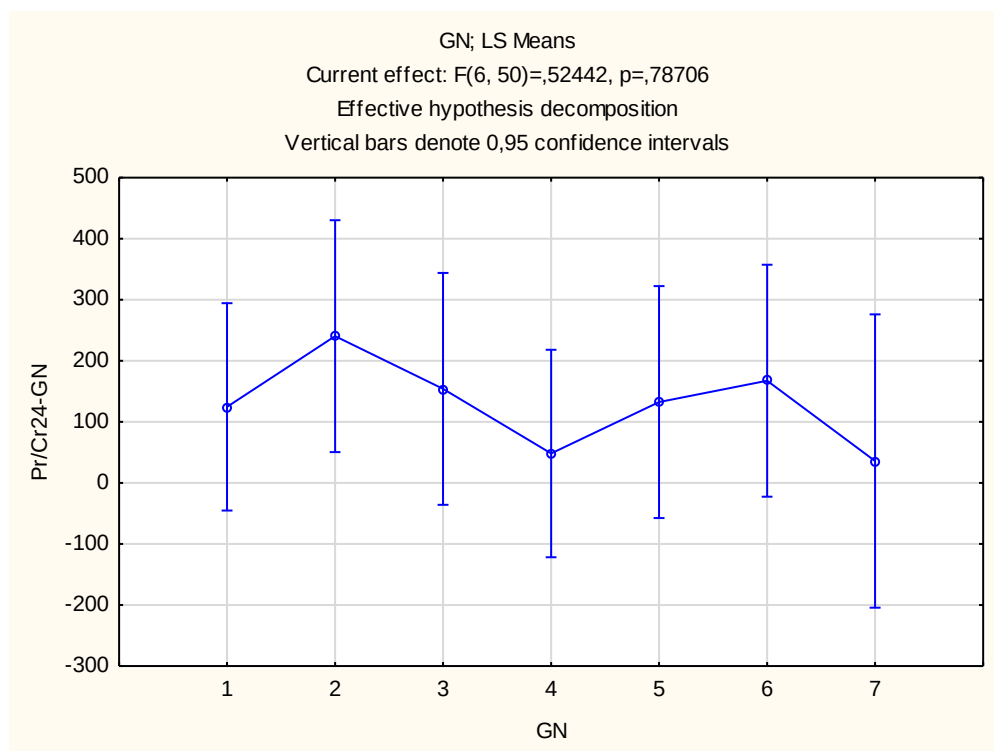


Figure 4. Analysis of variance (ANOVA) assessing differences in mean protein-to-creatinine ratio (Pr/Cr) at month 24.

The analysis of variance (ANOVA) demonstrated no statistically significant differences in the mean protein-to-creatinine ratio (Pr/Cr) at baseline across the study groups ($p > 0.05$). This finding indicates that the groups were comparable at the start of the follow-up period, allowing for a reliable assessment of subsequent changes over time.

At month 24, ANOVA revealed a statistically significant difference in mean Pr/Cr values between the study groups ($p < 0.05$). This suggests a differential treatment response and/or disease progression among the groups during the follow-up period.

4. Discussion

The results obtained from the present follow-up demonstrate a clear trend toward a reduction in proteinuria among patients with chronic glomerular diseases during the course of therapy. Proteinuria is a well-established marker both of the activity of glomerular injury and of long-term renal prognosis. The degree of proteinuria is one of the strongest independent predictors of progression of chronic kidney disease and the development of end-stage renal failure [1,3,7]. For this reason, its reduction is considered a primary therapeutic goal in modern nephrology practice.

A significant subset of glomerular diseases included in this study is directly related to systemic rheumatologic conditions. Kidney-related symptoms in rheumatic diseases are often present, which increase mortality and morbidity of patients with rheumatic diseases [37]. For example, lupus nephritis represents one of the most severe organ manifestations of systemic lupus erythematosus and is characterized by immune complex deposition within the glomeruli, leading to proteinuria and progressive renal dysfunction. Similarly, ANCA-associated vasculitis frequently presents with rapidly progressive glomerulonephritis and significant proteinuria, reflecting active small-vessel inflammation. In addition, cryoglobulinemic vasculitis is associated with immune complex-mediated glomerular injury, while secondary amyloidosis [31], often seen in chronic inflammatory rheumatic diseases such as rheumatoid arthritis, leads to progressive proteinuria due to extracellular deposition of amyloid fibrils within the kidney. These conditions highlight the close interplay between systemic inflammation and renal involvement, further emphasizing the importance of proteinuria as a shared clinical endpoint.

In the present study, the baseline value of 24-hour proteinuria was within the nephrotic range. The presence of high baseline proteinuria is associated

with an increased risk of structural damage to the glomerular filtration barrier, as well as with the development of tubulointerstitial fibrosis, which plays a key role in the progression of chronic kidney disease [6,7].

During the course of treatment, a statistically significant reduction in proteinuria was observed as early as the third month of follow-up. Such an early therapeutic response is considered a favorable prognostic factor, since early reduction of proteinuria is associated with a slower decline in glomerular filtration and a lower risk of reaching end-stage kidney disease (8, 9). The reduction of proteinuria during the first months of treatment is a strong predictor of long-term therapeutic success, regardless of the morphological variant of the glomerular disease [4,8,9]. In addition, a decrease in proteinuria was also observed at the sixth month of follow-up, indicating a sustained effect of the administered therapy. Although the difference between the third and sixth months did not reach statistical significance, the trend toward gradual reduction in proteinuria remained clearly expressed. This likely reflects the combined effect of ongoing nephroprotective therapy, including blockade of the renin–angiotensin–aldosterone system, as well as immunosuppressive treatment in patients with immune-mediated glomerular diseases [11,12,17].

A particularly important observation is the substantial reduction of proteinuria to approximately 1.72 g/24 h at the twelfth month. Achieving proteinuria levels below 2–3 g/24 h is considered partial remission and is associated with a significant improvement in renal prognosis [9,10]. In many glomerular diseases, including IgA nephropathy and membranous nephropathy, reduction of proteinuria below these threshold values is associated with stabilization of renal function and slowing of chronic kidney disease progression [8–10].

The results of the present study are consistent with data from large clinical trials demonstrating that early and sustained reduction in proteinuria is a key factor in improving long-term renal outcomes. Achieving partial or complete remission of proteinuria is associated with a significantly lower risk of developing end-stage renal failure and the need for renal replacement therapy [8–10,17].

In our cohort, all patients received ACE inhibitors or ARBs (unless contraindicated) from the time of diagnosis, which likely contributed to the reduction in proteinuria. It is well established that RAAS blockade has a pronounced antiproteinuric effect; the REIN study demonstrated a ~40–50% reduction in proteinuria and slowing of eGFR decline with ramipril in

proteinuric nephropathies [33]. Our findings are consistent with these observations, as patients receiving ACEi/ARB therapy showed a marked reduction in Pr/Cr ratio.

For instance, patients with moderate proteinuria treated with supportive therapy alone (RAAS blockade, diuretics, statins) achieved a reduction in proteinuria from approximately 1.5–2 g/day to below 0.5 g/day within 6 months. In cases of persistent or resistant proteinuria (>1 g/day despite 3–6 months of optimal supportive therapy), immunosuppressive treatment was initiated in accordance with KDIGO recommendations [23]. The addition of corticosteroids resulted in further reduction in proteinuria [40].

In patients with IgA nephropathy and nephrotic syndrome, a 6-month corticosteroid regimen (including pulse and oral administration) led to remission or significant improvement, consistent with findings reported by Pozzi et al., who demonstrated a reduced risk of doubling of serum creatinine and proteinuria compared to controls [34].

Similarly, in focal segmental glomerulosclerosis (FSGS) and minimal change disease, where corticosteroids are the mainstay of therapy, a substantial reduction in proteinuria was observed. In minimal change disease, initial massive proteinuria (~10–15 g/day) nearly completely resolved after an 8-week course of high-dose prednisolone. In steroid-resistant FSGS, the introduction of calcineurin inhibitors (tacrolimus) resulted in a >50% reduction in Pr/Cr over 6 months, consistent with the reported ~60% remission rate with CNIs in resistant nephrotic syndrome.

Adjunctive therapies such as mineralocorticoid receptor antagonists (e.g., spironolactone) provided additional benefits. Patients treated with spironolactone (25 mg/day) showed a further reduction in Pr/Cr of approximately 20–30% compared to ACEi monotherapy, in agreement with data from Park et al., who reported over 40% reduction in proteinuria within 3 months when low-dose spironolactone was added to ARB therapy [35]. Although a slight increase in serum creatinine was observed in their study, no clinically significant deterioration in kidney function was noted in our cohort, likely due to careful monitoring.

The SGLT2 inhibitor dapagliflozin was administered in selected patients with IgA nephropathy and residual proteinuria. The observed additional reduction in Alb/Cr is consistent with findings from the DAPA-CKD trial, where dapagliflozin reduced albuminuria by approximately 26% compared to placebo [36].

Importantly, the degree of proteinuria reduction after 12 months of treatment is a critical predictor of long-term outcomes. Our data indicate that patients who achieved proteinuria <1 g/day at month 12 maintained stable kidney function without progression. This is consistent with previous studies, such as the Lupus Nephritis Maintenance Trial, which demonstrated that early reduction in proteinuria during the first year strongly predicts favorable long-term prognosis [2,9].

The analysis of the protein/creatinine ratio (Pr/Cr) in a spot urine sample further confirms the observed trend. This parameter is widely used in clinical practice as a convenient and reliable method for assessing proteinuria, although in glomerular diseases and at higher levels of protein excretion, its correlation with 24-hour proteinuria may be moderate rather than absolute [18,19]. In the present analysis, a significant reduction in Pr/Cr was observed even in the early stages of follow-up, corresponding to the observed decrease in 24-hour proteinuria.

The reduction in proteinuria is likely due to the combined effect of the different therapeutic regimens used in the patients. Blockade of the renin-angiotensin-aldosterone system represents a fundamental component in the treatment of proteinuric kidney diseases, as it reduces intraglomerular pressure and decreases protein filtration through the glomerular barrier [11,12]. Additionally, in some patients modern nephroprotective medications such as SGLT2 inhibitors were used; by restoring tubuloglomerular feedback and reducing glomerular hyperfiltration, these agents contribute to lowering proteinuria [13,14].

Immunosuppressive therapy also plays an important role in immune-mediated glomerular diseases. Suppression of the immunological mechanisms of glomerular injury leads to a reduction in inflammatory activity within the glomeruli and consequently to a decrease in proteinuria [1,17]. In diseases such as membranous nephropathy, lupus nephritis, and ANCA-associated glomerulonephritis, achieving remission of proteinuria is considered an important indicator of therapeutic success and better long-term prognosis [10,20].

In a broader clinical context, increasing interest is being directed toward the role of urinary biomarkers in other diseases of the urogenital system, including oncological urological conditions, which emphasizes the importance of early laboratory assessment for diagnosis, follow-up, and therapeutic monitoring [21].

Although the present study was not specifically designed for subgroup statistical analysis, a proportion of patients had glomerular diseases associated with systemic autoimmune conditions, including lupus nephritis and ANCA-associated vasculitis [38,39]. In these patients, the observed reduction in proteinuria paralleled clinical improvement, suggesting that proteinuria may serve as an indirect marker of systemic disease control.

In rheumatologic practice, proteinuria is increasingly recognized as a key therapeutic target, particularly in diseases such as systemic lupus erythematosus and systemic vasculitides. Current treatment strategies in lupus nephritis aim not only at immunological remission but also at achieving a significant reduction in proteinuria, often below 0.5–0.7 g/day, which is associated with improved long-term renal outcomes [22,27]. Similarly, in ANCA-associated vasculitis, reduction in proteinuria reflects control of glomerular inflammation and is used alongside other markers to monitor treatment response [29,30]. Therefore, proteinuria represents a clinically meaningful and measurable endpoint that bridges nephrology and rheumatology, allowing for integrated assessment of both renal and systemic disease activity.

These findings are consistent with rheumatology-focused studies demonstrating that early reduction in proteinuria predicts favorable renal outcomes in lupus nephritis (KDIGO 2021; EULAR/ERA-EDTA recommendations) [23-26]. EULAR recommendations for the management of systemic lupus erythematosus emphasize proteinuria reduction as a primary treatment goal in lupus nephritis [28].

The present study also has certain limitations. The heterogeneity of the included glomerular diseases, differences in the therapeutic regimens used, the relatively small number of patients and the absence of a control group may limit the ability to directly generalize the findings to all forms of glomerulopathies. In addition, the retrospective design is associated with potential biases and incomplete data. Despite these limitations, the study provides relevant real-world insights into the role of proteinuria as a marker of disease activity and therapeutic response and confirms the importance of early therapeutic intervention.

5. Conclusions

Proteinuria is a central biomarker of disease activity, severity, and progression in glomerular diseases, including those associated with systemic rheumatologic disorders. Beyond its role as an indicator of renal injury, proteinuria serves as an important therapeutic target and monitoring parameter in conditions such as systemic lupus erythematosus and systemic vasculitides. The present findings support the concept that early and sustained reduction in proteinuria is associated with improved renal outcomes and may reflect effective control of both renal and systemic disease processes. The reduction of proteinuria is increasingly recognized as one of the main therapeutic goals in the modern treatment of glomerular diseases, as well as a reliable indicator of the effectiveness of the applied therapy. These observations highlight the importance of an integrated nephrology–rheumatology approach in the management of patients with immune-mediated kidney involvement.

Author Contributions

Conceptualization: M.B., S.B.; Methodology: M.B., S.B.; Formal analysis: M.B.; Investigation: M.B.; Writing – original draft: M.B., S.B.; Writing – review & editing: all authors.

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Institutional Review Board Statement

The study was retrospective and statement from the Commission on Institutional Oversight was not necessary.

Informed Consent Statement

Informed consent was waived due to the retrospective nature of the study

Data Availability Statement

The data presented in this study are available on reasonable request from the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

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Протеинурията при имуномедиирани гломерулни заболявания като маркер за болестна активност и терапевтичен отговор: Ретроспективно проучване

Резюме

Въведение: Протеинурията е утвърден маркер за активността, тежестта и прогресията на гломерулните заболявания. Освен че отразява увреждането на гломерулната филтрационна бариера, тя играе и патогенетична роля в развитието на тубулоинтерстициално възпаление и фиброза. **Цели:** Да се оцени динамиката на протеинурията при пациенти с хроничен гломерулонефрит и нейното значение като индикатор за терапевтичен отговор. **Методи:** Проведено е ретроспективно проучване на общо 57 пациенти с различни морфологични форми на хроничен гломерулонефрит, лекувани в Клиниката по нефрология и диализа към УМБАЛ „Св. Марина“ – Варна и проследени за период от 24 месеца. Анализирани са 24-часовата протеинурия и съотношението протеин/креатинин (Pr/Cr) в еднократна уринна порция. Всички пациенти са получили оптимална нефропротективна терапия, а при наличие на показания е прилагано и имunosупресивно лечение. **Резултати:** Средната изходна 24-часова протеинурия възлиза на 5,94 g/24 h. До третия месец се наблюдава статистически значимо понижение до 3,65 g/24 h ($p \approx 0,008$), последвано от по-нататъшна редукция до 2,7 g/24 h на 6-ия месец и до 1,72 g/24 h на 12-ия месец. Наблюдаваното понижение е показател за ранен и устойчив терапевтичен отговор в изследваната популация пациенти. Анализът на съотношението протеин/креатинин потвърждава същата благоприятна тенденция и подкрепя неговата приложимост като надежден маркер за мониториране на протеинурията в клиничната практика. **Заключение:** Ранното и трайно намаляване на протеинурията е надежден индикатор за терапевтична ефикасност при хронични гломерулни заболявания и е свързано с по-благоприятна ренална прогноза. Протеинурията притежава съществена стойност както като прогностичен маркер, така и като сурогатен краен показател в клиничното проследяване.

Ключови думи: протеинурия, хроничен гломерулонефрит, хронично бъбречно заболяване, терапевтичен отговор