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Membranöz Nefropatili Hastalarda Prognostik Faktörler

Prognostic Factors in Membranous Nephropathy Patients

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Öz

GİRİŞ ve AMAÇ: Membranöz nefropati (MN) yetişkinlerde nefrotik sendromun (NS) en yaygın nedenidir.Çalışmamızda MN'li hastalarda 1. yıl sonunda remisyonu etkileyen faktörleri belirlemeyi amaçladık.
YÖNTEM ve GEREÇLER: Retrospektif çalışmamız, 2015-2018 yılları arasında MN tanısı almış, 18 yaş üstü hastalar üzerinde gerçekleştirildi. Hastalara ait tüm veriler hastanemiz medikal kayıtlarından elde edildi. MN hastaların başlangıç, 6., 12. ay laboratuvar değerleri (serum albümin, proteinüri, eGFR) ve 12. ay sonunda tedavi yanıt durumu değerlendirildi..
BULGULAR: Çalışmamızda ortalama yaşı 42.2±12.5 olan 24(%55.8)'u kadın 43 MN'li hasta üzerinde gerçekleştirildi. Hastalar 12 aylık tedavi süresinin sonunda remisyona giren (22, %51.2) ve girmeyen (21, %48.8) olmak üzere 2 gruba ayrıldı. Remisyon grubunda kadın cinsiyet daha fazla (p = 0,022), diyastolik kan basıncı daha düşük (p=0,025), mikofenolat kullanımı daha az (p=0,019), serum kreatinin daha düşük (p<0,001), eGFR daha yüksek (p=0,008), LDL (p=0,039), HDL (p=0,035), eritrosit sedimantasyon hızı (ESR) (p=0,012) ve CRP (p=0,016) düzeyleri daha yüksek saptandı. Tedavi yanıtı değerlendirildiğinde proteinüri 6. (p<0.001) ve 12. ayda (p<0.001), serum albumini ise 12. ayda (p<0.001) remisyona giren grupta girmeyenlere göre daha düşük seviyede saptandı.
TARTIŞMA ve SONUÇ: Tanı anında erkek cinsiyet, eGFR, diyastolik kan basıncı, LDL, HDL, ESR ve CRP, MN hastalarında birinci yılın sonunda remisyonu etkileyen faktörler olarak saptandı. Proteinüri, eGFR ve serum albümine göre tedaviye yanıtın daha erken bir göstergesi olduğunu söyleyebiliriz.
Anahtar Kelimeler: membranöz nefropati, nefrotik sendrom, proteinüri

Abstract

INTRODUCTION: Membranous nephropathy (MN) is the most common cause of nephrotic syndrome (NS) in adults. In our study, we aimed to determine the factors affecting remission in patients with MN at the end of the first year
METHODS: Our retrospective study was performed on patients over 18 years of age diagnosed with MN between 2015-2018. In MN patients, baseline, 6th, 12th-month laboratory values (serum albumin, proteinuria, eGFR) and treatment response at the end of the 12th month was evaluated.
RESULTS: Forty-three MN patients (24 (55.8%) women) with a mean age of 42.2±12.5 were evaluated. MN patients were divided into two groups at the end of the 12-month treatment period, remission and non-remission. In the remission group, female gender was higher (p=0.022), diastolic blood pressure was lower (p=0.025), mycophenolate use was less (p=0.019), serum creatinine was lower (p<0.001), eGFR was higher (p=0.008), LDL (p=0.039), HDL (p=0.035), erythrocyte sedimentation rate (ESR) (p=0.012) and CRP (p=0.016) levels were higher. In patients in remission, proteinuria was found at a lower level at sixth (p<0.001) and 12th months (p <0.001), and serum albumin at 12th months (p <0.001) compared to non-remission patients.
DISCUSSION AND CONCLUSION: At the time of diagnosis, the male gender, eGFR, diastolic blood pressure, LDL, HDL, ESR, and CRP are factors that can affect remission at the end of the first year in MN patients. We can say that proteinuria is an early indicator of response to treatment than eGFR and serum albumin.
Keywords: membranous nephropathy, nephrotic syndrome, proteinuria

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INTRODUCTION

Membranous nephropathy (MN) is among the common causes of nephrotic syndrome (NS) in adults (1). It is the second most common primary glomerular disease in Turkey (2). The disease may present from subnephrotic proteinuria to severe proteinuria and NS. One-third of patients go into spontaneous remission, another third develops chronic proteinuria, and the remaining one-third has end-stage renal disease (ESRD). Untreated MN can lead to ESRD in up to 20-30% of patients (3).

Thrombospondin type 1 containing M-type phospholipase A2 receptor-1 (PLA2R), 7A (THSD7A), and the recently described neural epidermal growth factor-like 1 protein are the major podocyte antigens found in MN (NELL-1) (4-6). Poor prognostic factors were reported as male gender, advanced age (> 50 years), hypertension, proteinuria (> 10 g/day), and increased serum creatinine concentration at the time of kidney biopsy and presence of severe damage findings in kidney biopsy (7-9).

General supportive treatment in all MN patients consists of dietary sodium and protein restriction, blood pressure control, reduction of proteinuria with renin-angiotensin system inhibition (RAAS), treatment of dyslipidemia. Immunosupresipressive treatment in MN patients should be considered in patients with a high risk of progressive disease or severe NS. (10, 11). MN patients can be managed better by determining risk factors for progression. We aimed to determine the factors affecting remission in MN patients at the end of the first year.

MATERIAL AND METHOD

Patient and samples

In this study, there were 43 patients with MN by kidney biopsy between 2015 and 2018. Patients were older than 18 years of age. The patients' demographic, clinical, laboratory and treatment data were collected from hospital outpatient records.

Age, gender, body mass index, alcohol use, smoking, systolic, and diastolic blood pressure (DBP) measurements, antihypertensive drugs, and systemic diseases were recorded at the time of diagnosis.

Laboratory tests including serum glucose, calcium, blood urea nitrogen (BUN), total protein, ALT, AST, sodium, uric acid, complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), HbA1C, total cholesterol, HDL, LDL, triglyceride evaluated on baseline (simultaneously with kidney biopsy). Proteinuria, creatinine, and albumin were recorded on the baseline, sixth, and 12th. According to the Chronic Kidney Disease Epidemiology Collaboration(CKD-EPI), the glomerular filtration rate (GFR) was assessed (12).

Treatment protocols

All patients received general supportive therapy. Salt restriction, diet, and, if appropriate, maximum dose of ACE (Angiotensin-converting enzyme inhibitor) ARB and (Angiotensin receptor blocker) treatment was given. Patients receiving immunosuppressive therapy, firstly oral methylprednisolone 0.5 mg/kg/day for 4 months, after that, dosage adjustments based on clinical response and lasted for at least six months. In addition to steroid therapy, cyclophosphamide, mycophenolate mofetil (MMF), and/or cyclosporine (2-3 mg/kg/day) were added to the therapy according to response to prednisolone therapy. Cyclophosphamide was given as monthly intravenous (IV) 0.5-0.75 g/m2 (maximum 1 g) for 6 months. MMF was administered at a dose of 2x500 /day and 2x1 /day according to body weight <50 kg and > 50 kg, respectively. Rituximab has given 375 mg/m2/week/IV x4 doses in 4 patients unresponsive to these treatments. A patient who did not take MMF due to side effects was given azathioprine (2 mg/kg/day).

Definitions

According to proteinuria in the 12th month, the patients were divided into remission and non-remission. In the remission group, proteinuria was defined as <300 mg/day and stable renal function; all other conditions were accepted as non-remission.

Pathological evaluation

Light and immunofluorescence microscopy was used to examine renal tissue samples. Hematoxylin and eosin (H&E), Jones methenamine silver, crystal violet, periodic acid-Schiff, Masson trichrome, and congo red histochemical stains were used on all renal tissue samples. Antibodies against IgM, IgA, IgG, C4, C3, C1q, lambda, kappa and fibrinogen were used to stain renal tissue sections. Electron microscopic examination was performed in some cases. MN was diagnosed according to the KDIGO glomerulonephritis guideline by two separate nephropathologists(13).

Ethics Committee

The ethics committee at Çukurova University's Faculty of Medicine approved our research (Date: 22 January 2021, number: 107-34).

Statistical analysis

IBM SPSS 21 (Chicago, IL, USA) was used as a statistical method. Differences between groups were compared using the Student T-test, Mann-Whitney U test and Chi-Square test. The differences in the 1-year follow-up of the groups that were in remission and non-remission were made with 2-way Repeated Measurement ANOVA. A significant value was described as $p<0.05$.

RESULTS

In our study, 43 MN patients (24 (55.8%) women) with a mean age of 42.2 ± 12.5 were evaluated. The clinical, laboratory, and demographic characteristics of the patients are shown in tables 1 and 2. According to proteinuria in the 12th months, the patients were divided into two groups: remission (22, 51.2%) and non-remission (21, 48.8%) (Table 3). Some finding as higher female gender (p=0.022), lower DBP (p=0.025), less MMF usage (p=0.019), lower serum creatinine level (p<0.001), higher eGFR (p=0.008), higher LDL cholesterol (p=0.039), higher HDL cholesterol (p= 0.035), higher ESR (p= 0.012) and higher CRP (p=0.016) levels were found in remission group after 12 months comparing to non-remission group.

Proteinuria, eGFR, and serum albumin values baseline, sixth and 12th months of treatment are shown in figures 1, 2, and 3. There was no difference between eGFR change in the remission and non-remission groups during the 1-year follow-up ($F=(1.906,72.434)=0.034$, p=0.962) (Figure 1). There were no differences between baseline, sixth, and 12th-month eGFR in both the remission and non-remission groups (p=0.259, p=0.069, respectively).

Table 1: Clinical, laboratory and demographic characteristics of the patients (n=43)

Parameters		mean + SD or (min-max), n(%)
Age, year		45.2±12.5 (18-68)
Male/female, n(%)		19 (44.2) / 24(55.8)
BMI, kg/m^2		26.9±4.6 (20.1-42.2)
Smoking, n(%)		14 (32.6)
Alcohol n(%)		3 (7)
Hypertension, n(%)		21 (48.8)
ACEI / ARB, n(%)		35 (81.4)
SBP, mmHg		129.4±21.5 (90-180)
DBP, mmHg		80.7±13 (60-110)
Immunosupressive treatment, n(%)		
	Steroid	38 (88.4)
	MMF	15(34.9)
	Cyclophosphamide	8(18.6)
	Cyclosporine	10(23.3)
	Rituximab	4(9.3)
	Azathioprine	1(2.3)
eGFR, ml/min/1.73m^2		
	Basal	103.5±34.4 (17-159)
	6th month	103.9±32.8 (6-149)
	12th month	95.8±36.9(3-155)
Serum albumin, gr/dl		
	Basal	2.21±0.81(0.9-4.2)
	6th month	3.4±0.68(0.80-4.16)
	12th month	3.74±0.55(2.46-4.80)
Proteinuria, mg/day		
	Basal	**6060(720-31218)**
	6th month	**973(56-20438)**
	12th month	**244(70-11776)**

BMI: Body mass ındex, ACEI: Angiotensin-converting enzyme inhibitory, ARB: Angiotensin receptor blocker, MN: Membranous nephropathy, CTD: Connective tissue disease, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, eGFR: estimated Glomerular filtration rate

Table 2: Laboratory findings of membranous nephropathy patients (n=43)

Parameters	mean + SD (min-max), n(%)
Glucose, mg/dl	93.1±10.4 (72-116)
HbA1C, %	5.4±0.42 (4.6-7)
Creatinine, mg/dl	0.85±0.63 (0.33-3.79)
T.protein, g/dl	5±1.12(3.2-8.6)
Uric acid, mg/dl	5.3±1.2 (3-8.6)
Na, mmol/l	137.9±2.5(133-143)
Calcium, mg/dl	8.3±0.7 (6.8-9.8)
Total Cholesterol, mg/dl	331±123(125-791)
LDL, mg/dl	236±105 (80-665)
HDL, mg/dl	47±15(22-92)
TG, mg/dl	241±134(66-562)
Hb, g/dl	13.2±1.8 (9.2-17.4)
Platelet, x10^3/µl	293±79(128-483)
WBC, x10^3/µl	7912±2066(4400-13900)
CRP, mg/dl	0.496±0.197 (0.110-0.990)
ESR, mm/hr	**29.8±18.5 (2-76)**

CRP: C-reactive protein, WBC: White-cell count, Hgb: Hemoglobin, ESR: Erythrocyte sedimentation rate, TSH: Thyroid-stimulating hormone.

Table 3: Comparison of patients' baseline findings according to remission status (n=43)

Parameters	Remission group (n=22)	Non-remission group (n=21)	p
Gender, m/f	6 (%27.3)/16(%72.7)	13(61.9)/8(%38.1)	0.022[3]
Age, year	42.2±13.2	48.3±11.2	0.107[1]
BMI, kg/m^2	27.3±4.6 (20.5-35.4)	26.6±4.6 (20.1-42.2)	0.601[2]
ACEI/ARB, y/n	18/4	17/4	1.000[4]
Systolic BP, mmHg	124.5±21.3	134.5±20.9	0.131[1]
Diastolic BP, mmHg	76.4±11.2	85.3±13.7	0.025[2]
Hypertension, y/n	8/14	13/8	0.094[3]
Immunosupresif treatment, y/n			
Steroid	21(%95.5)/1(%4.5)	17(%81)/4(%19)	0.185[4]
Cyclophosphamide	2(%9.1)/20(%90.9)	6(%28.6)/15(%71.4)	0.132[2]
MMF	4(%18.2)/18(%81.8)	11(%52.4)/10(%47.6)	0.019[2]
Cyclosporine	5(%22.7)/17(%77.3)	5(%23.8)/16(%76.2)	1.000[4]
Rituksimab	1(%4.5)/21(%95.5)	3(%14.3)/18(%85.7)	0.345[4]
Glucose, mg/dl	91.5±10.1	94.8±10.7	0.777[1]
HbA1C,%	5.4±0.26	5.4±0.55	0.749[1]
eGFR, ml/min/1.73m^2	116±28.3	101±35.6	0.008[2]
Creatinine, mg/dl	0.71±0.70	1.01±0.52	<0.001[2]
Uric acid, mg/dl	5.1±1.02	5.6±1.4	0.226[1]
T.protein, g/dl	5.1±1.14	4.9±1.12	0.885[2]
Albumin, g/dl	2.15±0.79	2.27±0.83	0.642[1]
Calcium, mg/dl	8.3±0.78	8.3±0.56	0.988[1]
Na, mmol/l	138.2±2.61	138.4±2.81	0.799[1]
T.cholesterol, mg/dl	363±134	296±104	0.061[2]
LDL, mg/dl	267±113	203±85	0.039[2]
HDL, mg/dl	51±18	41±9	0.035[1]
TG, mg/dl	235±126	248±145	0.751[1]
Hgb, g/dl	13.1±1.7	13.4±1.9	0.595[1]
WBC, x10^3/µl	7296±1715	8556±2241	0.089[2]
Platelet, x10^3/µl	294±88	291±70	0.903[1]
ESR, mm/h	36.6±19.1	22.7±15.3	0.012[1]
CRP, mg/dl	0.56±0.224	0.42±0.133	0.016[1]
Proteinuria, mg/day	6870±3615	7292±6246	0.734[2]
Hematuria, y/n	**1/21**	**4/17**	**0.185[4]**

1Student T-test, 2Mann Whitney U test, 3Chi-squared test, 4Fisher's Exact Test
ACEI: Angiotensin-converting enzyme inhibitors, ARB: Angiotensin receptor blocker, ESR: Erythrocyte sedimentation rate MMF: Mycophenolate mofetil, eGFR: estimated Glomerular filtration rate

There was a difference between serum albumin changes in the remission and non-remission groups during the 1-year follow-up (F=(2,80)=4.376, p=0.024) (Figure 2). Serum albumin levels were not statistically different between the two groups baseline (p=0.733) and at six months (p = 0.116) but 12 months (p<0.001). In the remission group, serum albumin change differed at baseline, 6, and 12 months. (p<0.001). This difference was found between baseline and six months (p<0.001), between baseline and 12 months (p <0.001), between 6 and 12 months (p <0.001).

There was a difference between proteinuria change in the remission and non-remission groups during the 1-year follow-up (F=(2,78)=10.231, p=0.002) (Figure 3). While baseline proteinuria in remission and non-remission groups was similar (p=0.426), there were differences in proteinuria between the two groups at sixth (p<0.001) and 12 months (p<0.001).

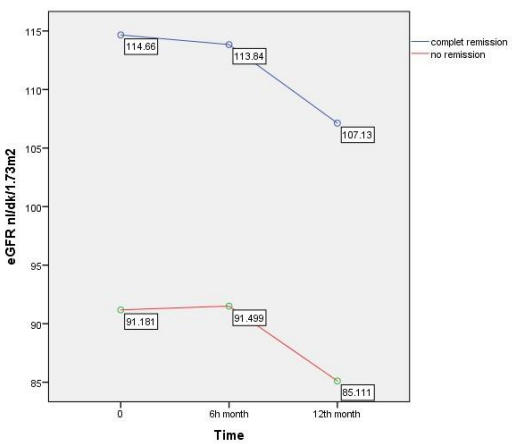

Figure 1: Change in patients GFR in the 12th month according to remission status (p=0.962)

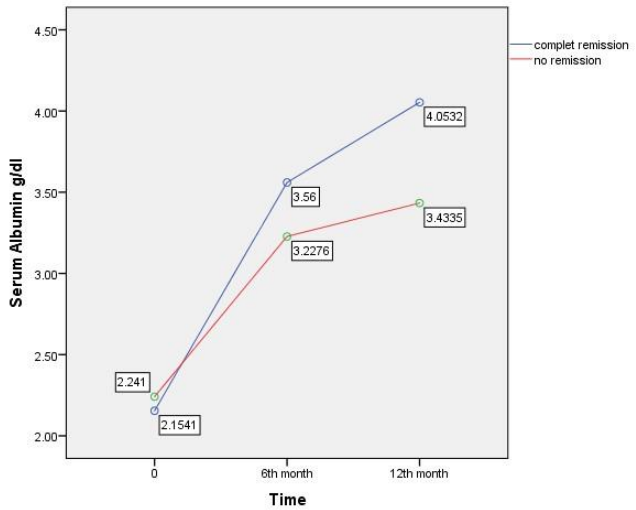

Figure 2: Change in patients serum albumin levels in the 12th month according to remission (p=0.024)

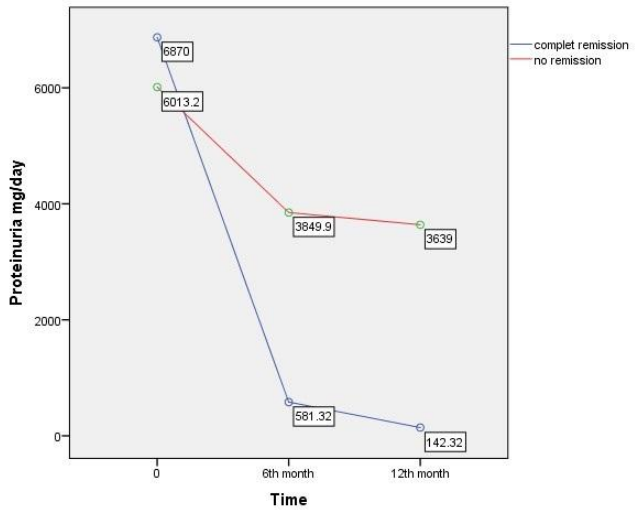

Figure 3: Change in patients proteinuria levels in the 12th month according to remission (p=0.002)

Proteinuria change in the remission group was different from each other at baseline, 6, and 12 months (p<0.001). This difference was found between baseline and 6 months (p<0.001), between baseline and 12 months (p <0.001), between 6 and 12 months (p = <0.001). Proteinuria values were different at baseline, 6, and 12 months in the non-remission group (p<0.001). This difference was found between baseline and six months (p<0.001), between baseline and 12 months (p<0.001), between 6 and 12 months (p<0.001).

DISCUSSION

In the study, we compared the baseline, sixth month, and 12th-month eGFR, serum albumin, and proteinuria values in MN patients in remission and non-remission at the end of 1 year. Among these two groups, the earliest difference among the three parameters was proteinuria level during the 1-year follow-up period. The proteinuria level between the two groups differed at 6 and 12 months, and serum albumin levels at 12 months. eGFR level did not differ between the two groups. These results indicate that the earliest indicator of treatment response in MN patients is proteinuria.

NS and preserved renal function are common in MN patients (14). The severity and duration of proteinuria are closely related to renal function loss, and persistent severe proteinuria is associated with poor renal survival (7, 15-17). For example, Cattran et al. reported that the 6-month highest proteinuria level is the most important parameter affecting long-term results (18). The main aim of therapy in MN is to reduce proteinuria. Complete reduction, identified as near-normal protein excretion (<0.3g/d)) while maintaining GFR, is associated with a low risk of relapse and long-term patient and kidney survival (19, 20). The amounts of proteinuria at the time of diagnosis were similar in both groups in our study. However, it was lower in the remission group than non-remission in the 6th month. This difference was not detected in serum albumin and eGFR. Proteinuria appears to be the earliest sign of remission in MN, according to our findings.

As in the study of Hyuk Huh et al., initial serum creatinine values were lower in our patients with remission (21). It has been reported that high serum creatinine (1.5 mg/dl) level at the time of diagnosis is a predictor for ESRD outcome (17). In another study, the initial eGFR value of <60 ml/min/1.73m2 increased the risk of ESRD (8). In a 10-year-follow study, the GFR decline rates of those in complete remission, partial remission, and non-remission were -0.12 ± 0.40, −0.17 ± 0.50, −0.86 ± 1.08 ml/min/month, respectively. Besides, kidney functions were better preserved in those who achieved complete remission or partial remission (22). In our study, serum creatinine values were within normal limits in patients with and without remission, and monthly eGFR loss was detected as 0.65 and 0.50 ml/min/month, respectively. There was no difference in eGFR change between the two groups for one year. Since our study's follow-up period was one year, it provided short-term information on the relationship between remission and eGFR.

In our study, after one year, women had a higher frequency of remission. Similarly, previous studies with MN patients have reported slower progression and better renal survival in women than men (17, 23-25). Moreover, this risk is independent of proteinuria, age, and blood pressure, which have prognostic importance (24). It has been reported that this difference may arise from nitric oxide or RAAS (26, 27).

Treatment in patients with idiopathic MN is alkylating agents combined with steroids or calcineurin inhibitors (28). MMF is not recommended as monotherapy for initial therapy (10). Adding MMF to calcineurin inhibitor treatment also does not reduce remission duration and relapse frequency (29). However, MMF may help reduce proteinuria in some patients who are resistant to therapy (30). Our study used MMF treatment in 3rd line therapy in MN patients who were unresponsive or intolerant to alkylating or calcineurin inhibitors. However, we found that it was ineffective in treatment.

At the time of initial diagnosis, high blood pressure is a poor

prognostic factor in MN patients (7, 9). MN patients with hypertension have lower cumulative renal survival than those without (31). In particular, DBP is an independent risk factor for ESRD development (31). In our study, supporting that DBP is a poor prognostic marker in MN, the non-remission group had higher DBP before treatment. In chronic glomerulonephritis, high blood pressure may be caused by excessive volume, RAAS, and sympathetic nervous system activation (32).

Importantly, baseline ESR and CRP, which are inflammation markers, were higher in the non-remission group. We did not classify patients as primary or secondary MN, but this may be related to etiological factors such as infection, malignancy, vasculitis, or systemic disease (33). It may also reflect the severity of the underlying inflammatory disease (34).

Lipids are important in the pathogenesis of proteinuria, according to studies in an experimental animal model of Heymann nephritis. Local reactive oxygen species create lipid peroxidation (LPO) products after the accumulation of subepithelial immune complexes, altering the structure of the glomerular basement membrane. In rats with Heymann nephritis, the LPO inhibitor probucol can reduce urinary protein excretion. As a result, hyperlipidemia can play a role in glomerular injury in MN (35). In mesangial cells, LDL cholesterol induces hypertrophy (36, 37). Also, LDL can undergo the oxidation process in both mesangial cells and macrophages (38, 39). LDL can activate the formation of endothelin, thromboxane, and angiotensin II (40, 41). Oxidized LDL may contribute to vasoconstriction by reducing nitric oxide in glomeruli. A limited number of studies have reported that lowering lipid levels may slow kidney disease progression (42). Low serum HDL levels are a predictor of accelerated GFR loss in patients with chronic kidney disease (43). In our study, baseline LDL and HDL values were higher in the remission group than the non-remission group. Hyperlipidemia, which is part of the nephrotic syndrome, is also a sign of severe proteinuria and makes it more complicated.

However, we found no difference between basal proteinuria and serum albumin values in patients with and without remission. On the other hand, it has been reported that there is no benefit of lipid-lowering on the progression of proteinuric chronic kidney disease (44). Studies are insufficient to comment on this subject; more comprehensive studies are required.

The limitations of our study are the retrospective, single-center, and insufficient number of patients.

We can say that in MN patients, gender, eGFR, DBP, serum levels of LDL and HDL, ESR, and CRP at the time of diagnosis were prognostic markers for remission at the end of the first year. Proteinuria was an early response indicator in disease follow-up.

Ethics Committee Approval: Çukurova Üniv. 107/34/22.01.2021
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