http://www.jnephropharmacology.com DOI: 10.15171/npj.2020.09

Journal of Nephropharmacology

Morphologic lesions of membranous nephropathy in association with various demographic and laboratory parameters of patients; a single center study

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ARTICLE INFO

Article Type:
Original

Article History:
Received: 8 May 2019
Accepted: 11 July 2019
Published online: 27 July 2019

Keywords:
Membranous nephropathy
Nephrotic syndrome
End-stage renal disease
Glomerular basement membrane
Glomerular filtration rate
Phospholipase A2 receptor

ABSTRACT

Introduction: Nephrotic syndrome is an important clinical presentation of glomerular diseases that is classified into several types based on the findings of renal biopsy. Membranous neuropathy is the most common cause of nephrotic syndrome, especially in adults over 40 years of age, which may lead to end-stage renal failure.

Objectives: The present study aimed to assess the association of morphologic lesions of membranous nephropathy (MN) on renal biopsy with various demographic and laboratory parameters of the patients.

Patients and Methods: This study was performed on renal biopsies, which were referred to the laboratory with the diagnosis of MN. To reach a definite diagnosis of MN, an immunofluorescence study (IgG, IgA, IgM, C1q and C3 antibody deposits) was conducted for all patients. Light microscopy was conducted to categorize the morphologic lesions of the glomeruli and interstitial area. The percentage of interstitial fibrosis/tubular atrophy was assessed too. Additionally, age, gender, and 24-hour urinary protein and serum creatinine were recorded.

Results: Among 175 idiopathic MN patients, 98 were male (56%). The patients' age was between 14 and 84 years (mean; 42±15 years). The mean of serum creatinine and 24-hour urine protein were 1.05 ± 0.31 mg/dL and 2779.56± 1495.80 mg/d, respectively. We found a significant correlation between gender and serum creatinine level, which was higher in men ($P<0.001$). Moreover, there was a significant, positive correlation between serum creatinine and age of patients ($P<0.001$, r=0.25). Additionally, there was a significant correlation between serum creatinine and interstitial fibrosis ($P=0.001$). We found a significant correlation between serum creatinine and the pathologic stage of glomeruli ($P=0.003$). The stages of glomeruli were also associated with the proportion of interstitial fibrosis ($P=0.001$) and C3 deposition rate ($P=0.002$). IgG deposition score was also significantly different in age ranges over and under 40 years of age ($P=0.001$). The 24-hours proteinuria had no correlation with other laboratory parameters and microscopic findings.

Conclusion: In accordance with other studies, we found that MN is more common among male patients. The positive correlation between serum creatinine and proportion of interstitial fibrosis is in concordance with previous studies. We found a positive correlation between serum creatinine and glomerular morphologic stages. It may show the importance of glomerular damage intensity in prognosis and survival of patients.

Implication for health policy/practice/research/medical education:
In a study on 175 idiopathic membranous nephropathy patients, we found that MN is more common among male patients. The positive correlation between serum creatinine and proportion of interstitial fibrosis is in concordance with previous studies. We found a positive correlation between serum creatinine and glomerular morphologic stages. It may show the importance of glomerular damage intensity in prognosis and survival of patients.

Please cite this paper as: Zamani S, Nasri H. Morphologic lesions of membranous nephropathy in association with various demographic and laboratory parameters of patients; a single center study. J Nephropharmacol. 2020;9(1):e09. DOI: 10.15171/npj.2020.09.

Introduction

Glomerular diseases are one of the most important causes of end-stage renal disease (ESRD) in both developed and developing countries, which are considered as the third most common cause of ESRD (after diabetes and hypertension) (1,2).

Nephrotic syndrome is an important type of glomerular disease that is classified into several subtypes based on renal biopsy findings, of which membranous nephropathy (MN) is the most common cause, especially in adults over

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40 years. Some studies show that MN could be considered as the cause of 35% of cases of nephrotic syndrome in adults (1,3). In 75% of adult patients, MN has been found in the form of an idiopathic disease (idiopathic membranous nephropathy; IMN) by an autoimmune glomerular disease mechanism, that is antibody-dependent. This antibody has been found in 70% of IMN patients and is produced against M-type phospholipase A2 receptor (PLA2R or phospholipase A2 receptor), which is the most important antigen produced by podocytes (3,4).

The rest of cases, about 25%, could have secondary systematic causes such as drugs, such as penicillamine, gold components, anti-alpha TNA, captopril and non-steroidal anti-inflammatory drugs (NSAIDs), infections such as hepatitis B or C, autoimmune diseases such as systemic lupus erythematosus (SLE), thyroiditis, and malignancy (5).

The pathophysiology of this disease involves the deposition of immune complexes in the sub-epithelial space (7), and consequently podocytes disorder and thickening of capillary walls in the glomerular tuft (8).

Detection of this disease is by immunofluorescence microscopy of the renal biopsies which demonstrates IgG and C3 granular deposits in capillary walls and, light microscopy which shows thickening of glomerular basement membrane (GBM), pinhole and spikes (using silver staining), and sometimes fuchsinophilic immune-complex deposits (using trichrome staining). The electron microscopy shows sub-epithelial immune complex deposits (3,9-13).

MN affects both genders and all races (14). Age, renal function, gender, levels of proteinuria, presence of hypertension, and values of serum albumin and creatinine predict high-risk patients (10,15,16).

The higher level of proteinuria tends to raise the risk of renal failure, since, almost one-third of IMN cases progress to ESRD. The complications of IMN could be due to nephrotic syndrome. These complications could be thrombotic, and thromboembolic episodes that occur when serum albumin levels are lower than 2.8 g/dL. Thromboembolic episodes increase morbidity and mortality in MN (10,15,17,18).

Male gender, age over 50 years, proteinuria more than 10 g/24 h, and elevated serum creatinine are factors for disease prognosis at the beginning of IMN. Age over 60 years, serum albumin lower than 25 g/dL, and interstitial fibrosis more than 25% are also risk factors predicting ESRD in IMN patients (19, 20).

The treatment of MN is highly challenging, with one-third of patients undergoing spontaneous remission during first year of the disease, one-third progress to ESRD. Routine treatment for these patients includes immunosuppressive drugs and corticosteroids that are recommended for all of them. These drugs have various complications including carcinogenesis and increased risk of infectious diseases. Therefore, it is recommended to administer these drugs only to high-risk patients (21-23). If we can recognize high-risk patients at the early stages by renal biopsy and detect, the correlation between morphologic lesions and the demographic and laboratory factors, then we will be able to specify suitable immunosuppressive for them (21).

Objectives

The aim of the present study was to assess the association of morphologic lesions of MN patients with various demographic and laboratory parameters.

Patients and Methods

Study population

This cross-sectional study (2011 to 2018) was conducted on renal biopsies referred to a laboratory in Isfahan, Iran. Biopsies were assessed using both light and immunofluorescence microscopies. Two samples were obtained from each patient (for light and immunofluorescence microscopies), and were sent to the laboratory in formalin and normal saline and on ice for light and immunofluorescence (IF) studies, respectively. IF slides (stained for IgG, IgA, IgM, C1q and C3 antibodies) and four light microscopy slides (stained for H&E, Masson's trichrome, PAS and Jones' methenamine silver) all were prepared and were assessed by one nephropathologist. It should be mentioned that Jones' methenamine silver stain was used to find spikes on the outer aspect of the glomerular capillaries, whereas other stains were used to assess interstitial fibrosis and glomerulus morphology. Inclusion criteria for patients were the presence of at least 8 glomeruli in each biopsy.

In IF microscopy, granular deposits of IgG and C3 were seen on the outer surface of capillary wall, since deposits of C1q implied the secondary MN like lupus nephritis, class 5. Hence, the presence of significant C1q deposits was an exclusion criterion, Moreover, to validate IMN on light microscopy, there must be no proliferation/hypercellularity in mesangial, endothelial, or extracapillary areas (10).

Morphologic lesions of IMN on light microscopy included GBM thickening, presence of pinhole and spikes using silver staining (often), and fuchsinophilic deposits on trichrome staining (sometimes) (10). Histopathologic stages and percentage of interstitial damages were determined. MN has four pathologic stages on light microscopy as follows;

- Stage 1; when glomeruli are normal but IgG granular deposits are detectable.
- Stage 2; when there is vacuolization in GBM.
- Stage 3; spike is seen using silver staining.
- Stage 4; GBM is clearly thickened and become double contoured on light microscopy (6).

The intensity of IgG, IgM, and C3 deposits by IF study were classified semi-qualitatively; no deposits (0), scant deposits (trace), mild deposits (+1), medium deposits (+

2), and significant deposits (+ 3).

Interstitial fibrosis was quantified as three scores; less than 10% fibrosis (0), 10% to 25% fibrosis (1), 25% to 50% fibrosis (2), and more than 50% fibrosis (3) (24).

Therefore, the diagnosis of MN was conducted by both light and IF microscopies, since the histopathologic stages of the glomerulopathy were detected using light microscopy.

Accordingly, age, gender, 42-hour urinary protein level and serum creatinine was recorded. Likewise, the proportion of totally sclerotic glomeruli and interstitial damage (interstitial fibrosis/tubular atrophy) were recorded.

Ethical considerations

The research followed the tenets of the Declaration of Helsinki. In this research, we followed all the ethical considerations related to research on patients' clinical samples. The study was approved by the Research Committee and the Ethical Committee of Isfahan University of Medical Sciences. This study was extracted from M.D thesis of Sara Zamani in Isfahan University of Medical Sciences (#396363).

Statistical analysis

The collected and modified data were analyzed by using IBM SPSS Statistics 24 software. To provide the results for quantitative variables, statistical indices including central and dispersion, and for qualitative variables, tales and percentage of frequency were used. Statistical analysis was performed using appropriate statistical tests such as Mann-Whitney, Kruskal-Wallis, chi-square and Fischer's exact tests. In this study, *P* values less than 0.05 were considered statistically significant.

Results

Out of all conducted renal biopsies, 186 samples showed MN, of which, 11 samples were excluded from the study since they were secondary. Thus, 175 patients were analyzed.

Among 175 patients, 98 cases (56%) were male with a male to female ratio of 1.27 to 1.

In this study, the age range was 14 to 84 years. The mean age of patients was 42 ± 15 years with an average of 44 ± 15 and 40 ± 14 years for men and women, respectively. Ninety patients (51%) were under 40 years old while, 85 patients (48%) were over 40 years old.

The mean of serum creatinine was 1.06 ± 0.31 mg/dL, with a range from 0.5 to 2.5 mg/dL. The mean 24-hours proteinuria was 2779.56 ± 1495.80 mg/d.

Around 164 patients (93.7%) had lower than 10% interstitial fibrosis, 9 patients (5%) had 10-25% fibrosis, and 2 patients (1.1%), had 26-50% interstitial fibrosis. Additionally, 18 patients (10%) had +2 IgG granular deposits, while 157 patients (89%) cases had +3 IgG granular deposits. Moreover, 31 patients (17%) did not have C3 granular deposits, 94 patients (53%) had +1 granular deposits of C3, 38 patients (21%) had +2 granular deposits of C3, and, 12 patients (6.9%) had +3 granular deposits of C3. In addition,132 patients (75%) did not have IgM deposits, 35 patients (90%) had +1 IgM deposits, while 7 patients (4%) had +2 IgM deposits.

Regarding the small number of patients in stage 4 (two patients), this stage was merged with stage 3 in the next steps of clinicopathologic correlation analysis.

This study showed, stage 1 (glomerular morphology) in 94 patients (53.7%), was the most common stage, and stages of 2, 3, and 4 were seen in 62 patients (35.4%), and 19 patients (11%) (stages 3 and 4), respectively. Table 1 shows patients' data.

Our study showed a significant, positive correlation of age with serum creatinine ($P=0.001$, r=0.25). However, mean of serum creatinine between two age groups over and under 40 years old had no significant difference ($P=0.29$).

No significant correlation between gender and the intensity scores of C3, IgG and IgM deposits, and also with proportion of interstitial fibrosis was found. We also

Table 1. Characteristics of patients (N = 175)

Variables	
Age (y), mean ± SD	42.4±15.24
Serum creatinine (mg/dL), Mean ± SD	1.06±0.31
Proteinuria (mg/d), Mean ± SD	779.56±1495.80
Age (y), No. (%)	
< 40	90 (51.4)
≥40	85 (48.6)
Gender, No. (%)	
Male	98 (56.0)
Female	77 (44.0)
Glomerular morphologic stages, No. (%)	
Stage 1	94 (53.7)
Stage 2	62 (35.4)
Stage 3,4	19 (10.9)
IgM, No. (%)	
0+	132 (75.9)
1+	35 (20.1)
2+	7 (4.0)
IgG, No. (%)	
2+	18 (10.3)
3+	157 (89.7)
C3, No. (%)	
0+	31 (17.7)
1+	94 (53.7)
2+	38 (21.7)
3+	12 (6.9)
Interstitial fibrosis, No. (%)	
<10%	164 (93.7)
10%-25%	9 (5.1)
26%-50%	2 (1.1)

found a significant correlation between serum creatinine and gender ($P=0.001$), glomerular morphology stage ($P=0.003$), and proportion of interstitial fibrosis ($P=0.001$). This study showed mean serum creatinine to be higher in men and increasing with the increase in morphologic stage or proportion of interstitial fibrosis (Table 2). No significant correlation between the mean of proteinuria/day with age, gender, or serum creatinine was found. Similarly, no significant correlation between the mean of proteinuria/day with proportion of interstitial fibrosis or C3, IgM, and IgG deposits was detected. In this study, we found a significant correlation between morphologic stages of the disease with intensity of interstitial fibrosis ($P=0.001$), and also with C3 deposit score ($P=0.002$). Around, 57% of patients with less than 10% of interstitial fibrosis were in stage 1, while 31% of patients with interstitial fibrosis were in stage 2, since around 10% of them were in stage 3.

Discussion

It has been consistently reported that the long-term outcomes of the IMN are different, and there is a need for reliable predictive factors to identify high-risk patients at early stages, to start immunosuppressive treatments specifically for them (12,13,25-27). Although numerous studies have already shown the importance of histological evaluation as the predictive factor for progression to renal failure in MN patients, other studies have revealed different results in the correlation of tissue changes with clinical presentations and laboratorial findings of the patients at the time of biopsy. However, they could not determine the tissue changes progression and the prognosis (28,29).

Table 2. Correlation between serum creatinine and variables

Variable		Serum creatinine (mg/dL)	P value
Gender	Male	1.15 ± 0.32	0.001
	Female	0.94 ± 0.25	
Age (y)	< 40	1.03 ± 0.26	0.296
	> 40	1.08 ± 0.35	
Glomerular stage	Stage 1	0.97 ± 0.20	0.003
	Stage 2	1.14 ± 0.39	
	Stage 3	1.19 ± 0.34	
IgM	0+	1.03 ± 0.29	0.148
	1+	1.17 ± 0.39	
	2+	0.97 ± 0.18	
IgG	2+	1.10 ± 0.36	0.743
	3+	1.05± 0.30	
C3	0+	1.03 ± 0.35	0.487
	1+	1.03 ± 0.25	
	2+	1.12 ± 0.40	
	3plus	1.11 ± 0.31	
Interstitial fibrosis	<10%	1.03 ± 0.27	0.001
	10%-25%	1.38 ± 0.38	
	26%-50%	2.15 ± 0.21	

In this study, biopsy of 175 IMN patients was evaluated in terms of histopathological stage of the disease (glomerular morphology), interstitial fibrosis stage, and IF findings such as C3, IgM, and IgG, and their correlation with age, gender, and laboratory parameters, such as proteinuria and serum creatinine level.

IMN can be considered as the most common cause of nephrotic syndrome in adults (30). However, insufficient studies have been performed so far to determine predictive risk factors for prognosis of the disease. Besides, the results of the Asian patients are not similar to the other populations (16,31). Almost 80% of MNs were idiopathic and 20% were secondary MN (32). We had 186 patients with the diagnosis of MN, and 175 of them (94%) were idiopathic, while secondary cases were excluded from the study. In our study, 56% were men and 44% were women. In other studies, also the number of affected men were approximately two times higher than women (7). IMN tends to occur in all ages; however, around 10% of patients were children. The age peak of the patients was 30 to 50 years, that was in concordance with our study, in which the mean age of the patients was 42 ± 15 years (38-43 years). Recent studies showed a 30% decrease in glomerular filtration rate during 2 years, and higher serum creatinine was correlated with the disease progression to ESRD (16). In this study, serum creatinine level was correlated with gender since it was more elevated in men, and accordingly it increased as the age raised. Serum creatinine was also correlated with the morphological stage of the glomeruli, as the stage of the glomeruli was higher, serum creatinine was also elevated.

In most of the studies, interstitial fibrosis/tubular atrophy is an important predictive factor for progression of IMN patients to renal failure (26,38). For example, in a study on 334 IMN patients, Wehrmann et al showed that tubule-interstitial fibrosis stage could act as a predictive factor for progression of IMN to ESRD (26,38). The study of Zhang et al conducted on 73 patients showed that more than 25% tubule-interstitial fibrosis could be a predictive risk factor for progression of IMN to ESRD (16). The study of Troyano et al on 389 IMN patients indicated that the damage rate and tubule-interstitial fibrosis were correlated with age and gender, while patients with more interstitial fibrosis had higher ages and lower creatinine clearance. However, no correlation has been found between interstitial fibrosis and proteinuria rate (39). In our study, patients with higher glomerular histopathologic stages had higher interstitial fibrosis percentage. Besides, fibrosis as a validated predictive factor in prognosis of the patients, had a positive correlation with serum creatinine at the time of biopsy, since in patients with higher interstitial fibrosis percentage, the mean serum creatinine was also higher.

Our study, in line with the study of Zhang et al (16)

showed that the glomerular stage one was the most common stage. There was a significant correlation between pathologic stages with serum creatinine and C3 deposit score, as well as interstitial fibrosis percentage. Proportion of patients with less than 10% interstitial fibrosis decreased as the stage of the disease increased, since, more than 25% interstitial fibrosis was more common in stages 2 and 3.

More recent studies showed, 80% of IMN patients had nephrotic range proteinuria (more than 3.5 g/d) with hypoalbuminemia, edema, hyperlipidemia, lipiduria, and normal or slightly decreased renal function. Around, 20% of patients had non-nephrotic range proteinuria (32, 40-43). In the present study, the mean of 24-hours proteinuria was 2779.56 ± 1495.80 mg/d.

The previous studies such as Honkanen et al and Ponticelli et al showed that the long-term prognosis of the IMN patients that had non-nephrotic range proteinuria was good (43-45). However, the study of Hladunewich et al reported that the prognosis of the disease was poor even in patients who had, non-nephrotic range proteinuria (43). In the study of Zhang et al, no significant correlation between proteinuria in the range of nephrotic syndrome and the prognosis of disease was found too (16). The cohort study of Yamaguchi et al in Japan on 171 IMN patients showed, that if the proteinuria was kept in lower level, it could be more effective in the survival of the patients (22). In our study, no correlation was found between the level of proteinuria and demographic, laboratory parameters, glomerular pathologic stage, and IF microscopy parameters.

IMN is a glomerular autoimmune disease, where the evaluation of glomeruli with light microscopy may be normal in the early stages. However, as the time passes, alterations of basal membrane and its thickening, and production of sub-epithelial spikes in basal membrane, and in outer layers of glomerular capillary wall develop. In IF microscopy, IgG granular deposits are detectable on outer surface of capillary wall with complement components of C3. In the study of Doi et al (32), the correlations between C3 complement deposits and the quantity of proteinuria were reported. However, in our study, the 2+ and 3+ deposit scores of IgG in the age over 40 years was higher. When the stage of the disease progressed, the proportion of patients with lack of C3 deposits decreased, while the proportion of patients with C3 with +3 deposit score increased.

Conclusion

Similar to other studies, we have shown that MN is more common in men. The positive correlation between serum creatinine and interstitial fibrosis in this study is also consistent with the results of previous studies. In this study, we detected a positive correlation between serum creatinine and pathological stages of the glomeruli. It can represent the importance of glomerular damage in the prognosis and survival of the patients.

Limitations of the study

This investigation was retrospective and was conducted at a single center. Besides, the study was cross-sectional without data on treatment or follow up to find the final outcome of patients. Thus, larger studies with multi-center cooperation are suggested.

Authors' contribution

HN reported the renal biopsies and edited the draft. SZ gathered the data and wrote the primary manuscript. All authors read, revised, and approved the final manuscript.

Conflicts of interest

The authors declare that they have no conflicts interest.

Ethical considerations

Ethical issues including plagiarism, double publication, and redundancy have been completely observed by the authors.

Funding source

None.

References

1. Perneger TV, Brancati FL, Whelton PK, Klag MJ. End-stage renal disease attributable to diabetes mellitus. Ann Intern Med. 1994;121:912-8. doi:10.7326/0003-4819-121-12-199412150-00002.
2. Smyth B, Haber A, Trongtrakul K, Hawley C, Perkovic V, Woodward M, et al. Representativeness of Randomized Clinical Trial Cohorts in End-stage Kidney Disease: A Meta-analysis. JAMA Intern Med. 2019. doi: 10.1001/jamainternmed.2019.1501.
3. Lai WL, Yeh TH, Chen PM, Chan CK, Chiang WC, Chen YM, et al. Membranous nephropathy: a review on the pathogenesis, diagnosis, and treatment. J Formos Med Assoc. 2015;114:102-11. doi: 10.1016/j.jfma.2014.11.002.
4. Kil BH, Zachariah T, Husain SA, Nestor J, Regunathan-Shenk R, Markowitz GS, et al. Membranous nephropathy in a patient with common variable immune deficiency. Kidney Int Rep. 2018; 3:738-742. doi: 10.1016/j.ekir.2017.12.002.
5. Oh YJ, Yang SH, Kim DK, Kang SW, Kim YS. Autoantibodies against phospholipase A2 receptor in Korean patients with membranous nephropathy. PLoS One. 2013;8:e62151. doi: 10.1371/journal.pone.0062151.
6. Glassock RJ. Diagnosis and natural course of membranous nephropathy. Semin Nephrol. 2003;23:324-32.
7. Pozdzik A, Brochériou I, David C, Touzani F, Goujon JM, Wissing KM. Membranous nephropathy and anti-podocytes antibodies: implications for the diagnostic workup and disease management. Biomed Res Int. 2018; 2018:6281054. doi: 10.1155/2018/6281054.
8. Santos FRL. Membranous glomerulonephritis: new insights in pathophysiology and therapeutic approach. J Bras Nefrol. 2014;36:59-62.
9. Lai WL, Yeh TH, Chen PM, Chan CK, Chiang WC, Chen

YM, et al. Membranous nephropathy: a review on the pathogenesis, diagnosis, and treatment. J Formos Med Assoc. 2015;114:102-11. doi: 10.1016/j.jfma.2014.11.002.
10. Fervenza FC, Sethi S, Specks U. Idiopathic membranous nephropathy: diagnosis and treatment. Clin J Am Soc Nephrol. 2008;3:905-19. doi: 10.2215/CJN.04321007.
11. Markowitz GS. Membranous glomerulopathy: emphasis on secondary forms and disease variants. Adv Anat Pathol. 2001;8:119-25.
12. Noel L, Zanetti M, Droz D, Barbanel C. Long-term prognosis of idiopathic membranous glomerulonephritis: Study of 116 untreated patients. Am J Med. 1979;66:82-90. doi: 10.1016/0002-9343(79)90486-8.
13. Zucchelli P, Ponticelli C, Cagnoli L, Passerini P. Long-term outcome of idiopathic membranous nephropathy with nephrotic syndrome. Nephrol Dial Transplant. 1987;2:73-8.
14. Schieppati A, Mosconi L, Perna A, Mecca G, Bertani T, Garattini S, et al. Prognosis of untreated patients with idiopathic membranous nephropathy. N Engl J Med. 1993; 329:85-9. doi:10.1056/NEJM199307083290203.
15. Diaz M, Agraz I, Soler MJ. Anti-phospholipase A2 receptor antibody and spontaneous remission in membranous nephropathy. Clin Kidney J. 2019;12:33-35. doi: 10.1093/ckj/sfy079
16. Zhang B, Cheng M, Yang M, Han S, Zhang Y-H, Shi H-G, et al. Analysis of the prognostic risk factors of idiopathic membranous nephropathy using a new surrogate end-point. Biomed Rep. 2016; 4:147-52.
17. Cattran DC, Brenchley PE. Membranous nephropathy: integrating basic science into improved clinical management. Kidney Int. 2017;91:566-74.
18. Li S-J, Guo J-Z, Zuo K, Zhang J, Wu Y, Zhou C-s, et al. Thromboembolic complications in membranous nephropathy patients with nephrotic syndrome-a prospective study. Thromb Res. 2012;130:501-5. doi: 10.1016/j.thromres.2012.04.015.
19. Glassock RJ. Diagnosis and natural course of membranous nephropathy. Semin Nephrol. 2003; 23:324-32.
20. Shiiki H, Saito T, Nishitani Y, Mitarai T, Yorioka N, Yoshimura A, et al. Prognosis and risk factors for idiopathic membranous nephropathy with nephrotic syndrome in Japan. Kidney Int. 2004;65:1400-7. doi: 10.1111/j.1523-1755.2004.00518.x.
21. Reichert LJ, Koene RA, Wetzels JF. Prognostic factors in idiopathic membranous nephropathy. Am J Kidney Dis. 1998; 31:1-11.
22. Yamaguchi M, Ando M, Katsuno T, Tsuboi N, Maruyama S. Urinary protein and renal prognosis in idiopathic membranous nephropathy: a multicenter retrospective cohort study in Japan. Ren Fail. 2018;40:435-41. doi: 10.1080/0886022X.2018.1487864.
23. Zhou X-J, Zhou F-D, Wang S-X, Zhao M-H. A case report of remission of refractory membranous nephropathy progressing to stage 4 chronic kidney disease using low-dose rituximab: A long-term follow-up. Medicine. 2018;97: e11184. doi: 10.1097/MD.0000000000011184.
24. Sethi S, D'Agati VD, Nast CC, Fogo AB, De Vriese AS, Markowitz GS, et al. A proposal for standardized grading of chronic changes in native kidney biopsy specimens. Kidney Int. 2017;91:787-9. doi: 10.1016/j.kint.2017.01.002.
25. MacTier R, Jones JB, Payton C, McLay A. The natural history of membranous nephropathy in the West of Scotland. Q J Med. 1986;60:793-802.
26. Wehrmann M, Bohle A, Bogenschütz O, Eissele R, Freislederer A, Ohlschlegel C, et al. Long-term prognosis of chronic idiopathic membranous glomerulonephritis. An analysis of 334 cases with particular regard to tubulo-interstitial changes. Clin Nephrol. 1989;31:67-76.
27. Murphy B, Fairley K, Kincaid-Smith P. Idiopathic membranous glomerulonephritis: long-term follow-up in 139 cases. Clin Nephrol. 1988;30:175-81.
28. Lee H, Koh H. Nature of progressive glomerulosclerosis in human membranous nephropathy. Clin Nephrol. 1993;39:7-16.
29. Yoshimoto K, Yokoyama H, Wada T, Furuichi K, Sakai N, Iwata Y, et al. Pathologic findings of initial biopsies reflect the outcomes of membranous nephropathy. Kidney Int. 2004;65:148-53. doi: 10.1111/j.1523-1755.2004.66027.x.
30. Hofstra JM, Fervenza FC, Wetzels JF. Treatment of idiopathic membranous nephropathy. Nat Rev Nephrol. 2013;9:443-58. doi: 10.1038/nrneph.2013.125.
31. Eriguchi M, Oka H, Mizobuchi T, Kamimura T, Sugawara K, Harada A. Long-term outcomes of idiopathic membranous nephropathy in Japanese patients treated with low-dose cyclophosphamide and prednisolone. Nephrol Dial Transplant. 2009;24:3082-8. doi: 10.1093/ndt/gfp251.
32. Couser WG. Primary membranous nephropathy. Clin J Am Soc Nephrol. 2017;12:983-997. doi: 10.2215/CJN.11761116.
33. Kanigicherla D, Gummadova J, McKenzie EA, Roberts SA, Harris S, Nikam M, et al. Anti-PLA2R antibodies measured by ELISA predict long-term outcome in a prevalent population of patients with idiopathic membranous nephropathy. Kidney Int. 2013;83:940-8. doi: 10.1038/ki.2012.486.
34. Glassock RJ. Pathogenesis of membranous nephropathy: a new paradigm in evolution. Contrib Nephrol. 2013;181:131-42. doi: 10.1159/000348472.
35. Ronco P, Debiec H. Advances in membranous nephropathy: success stories of a longjourney. Clin Exp Pharmacol Physiol. 2011;38:460-6.doi:10.1111/j.1440-1681.2011.05506.x.
36. Hofstra JM, Beck LH, Beck DM, Wetzels JF, Salant DJ. Anti-phospholipase A2 receptor antibodies correlate with clinical status in idiopathic membranous nephropathy. Clin J Am Soc Nephrol. 2011;6:1286-91. doi: 10.2215/CJN.07210810.
37. Ronco P, Debiec H. Pathogenesis of membranous nephropathy: recent advances and future challenges. Nat Rev Nephrol. 2012;8:203-13. doi: 10.1038/nrneph.2012.35.
38. Ponticelli C, Zucchelli P, PasseriniP, Cagnoli L, Cesana B, Pozzi C, et al. A randomized trial of methylprednisolone and chlorambucil in idiopathic membranous nephropathy. N Engl J Med. 1989;320:8-13. doi:10.1056/NEJM198901053200102.
39. Troyanov S, Roasio L, Pandes M, Herzenberg A, Cattran D. Renal pathology in idiopathic membranous nephropathy: a new perspective. Kidney Int. 2006;69:1641-8. doi:10.1038/sj.ki.5000289.
40. Guerry M-J, Vanhille P, Ronco P, Debiec H. Serum anti-PLA2R antibodies may be present before clinical manifestations of membranous nephropathy. Kidney Int. 2016;89:1399. doi: 10.1016/j.kint.2015.11.032.

41. Stanescu HC, Arcos-Burgos M, Medlar A, Bockenhauer D, Kottgen A, Dragomirescu L, et al. Risk HLA-DQA1 and PLA2R1 alleles in idiopathic membranous nephropathy. N Engl J Med. 2011;364:616-26. doi: 10.1056/NEJMoa1009742.
42. Ponticelli C, Glassock RJ. Glomerular diseases: membranous nephropathy—a modern view. Clin J Am Soc Nephrol. 2014;9:609-16. doi: 10.2215/CJN.04160413.
43. Hladunewich MA, Troyanov S, Calafati J, Cattran DC. The natural history of the non-nephrotic membranous nephropathy patient. Clin J Am Soc Nephrol. 2009; 4: 1417-22. doi: 10.2215/CJN.01330209.
44. Honkanen E, Törnroth T, Grönhagen-Riska C, Sankila R. Long-term survival in idiopathic membranous glomerulonephritis: Can the course be clinically predicted? Clin Nephrol. 1994;41:127-34.
45. Ponticelli C, Passerini P, Altieri P, Locatelli F, Pappalettera M. Remissions and relapses in idiopathic membranous nephropathy. Nephrol Dial Transplant. 1992;7:85-90.