Association of The Autoantibodies to M-Type Phospholipase A2 Receptor Titer with Clinical Characteristics and Outcome of Patients with Primary Membranous Nephropathy – 5-Year Follow up Study

Laganović, Mario; Horvatić, Ivica; Bubić, Ivan; Ilić, Mario; Maksimović, Bojana; Kozmar, Ana; Vuković Brinar, Ivana; Crnogorac, Matija; Živko, Marijana; Fištrek, Margareta; ...

Source / Izvornik: **Acta clinica Croatica, 2021, 60., 71 - 77**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

https://doi.org/10.20471/acc.2021.60.s1.11

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:184:204768

Acta Clin Croat (Suppl. 1) 2021; 60:71-77
doi: 10.20471/acc.2021.60.s1.11

Original Scientific Paper

ASSOCIATION OF THE AUTOANTIBODIES TO M-TYPE PHOSPHOLIPASE A2 RECEPTOR TITER WITH CLINICAL CHARACTERISTICS AND OUTCOME OF PATIENTS WITH PRIMARY MEMBRANOUS NEPHROPATHY – 5-YEAR FOLLOW UP STUDY

Mario Laganović[1], Ivica Horvatić[2], Ivan Bubić[3], Mario Ilić[4], Bojana Maksimović[5], Ana Kozmar[6], Ivana Vuković Brinar[1], Matija Crnogorac[2], Marijana Živko[7], Margareta Fištrek[6], Željka Jureković[5], Danica Galešić Ljubanović[2], Marijana Ćorić[1], Stela Bulimbašić[1], Krešimir Galešić[1] and Mladen Knotek[5]

[1]University Hospital Center Zagreb, Zagreb; School of Medicine, University of Zagreb, Zagreb;
[2]Dubrava University Hospital, Zagreb; School of Medicine, University of Zagreb, Zagreb;
[3]University Hospital Center Rijeka, Rijeka; School of Medicine, University of Rijeka, Rijeka;
[4]Dubrovnik County Hospital, Dubrovnik;
[5]Merkur University Hospital, Zagreb; School of Medicine, University of Zagreb Zagreb;
[6]University Hospital Center Zagreb, Zagreb;
[7]University Hospital Center Zagreb, Zagreb; School of Medicine, J.J. Strossmayer University of Osijek

SUMMARY – *Introduction:* primary membranous nephropathy (pMN) is glomerulopathy caused in the majority of cases by autoantibodies to Phospholipase-A2 receptors (PLA2R-AB). This study aimed to evaluate the clinical course and outcomes of the patients with pMN regarding PLA2R-AB status.

Patients and methods: 32 patients (21 males, 11 females) with renal biopsy-proven pMN were included in the study. PLA2R-AB (ELISA method) and outcomes (defined according to KDIGO) were evaluated after 21 and 64 months of follow-up in 28 patients.

Results: 19 patients had positive PLA2R-AB (>20 RU/ml) (59.3%), with median titer of 97 (21-1418 RU/ml). The rate of remission in low PLA2R-AB titer group (< 200 RU/ml) after 21 months was significantly higher than in high PLA2R-AB group (≥ 200 RU/ml) (90% vs. 50%, p=0.045), and after 64 months the difference was not significant (80% vs. 50%, p=0.210). The relapse rate after 64 months was higher in the high PLA2R-AB group (87% vs. 63%). Multivariant linear regression found serum creatinine (ß=0.682, p<0.001) and PLA2R-AB (ß=0.527, p<0.001) as significant predictors for kidney function at the end of follow-up.

Conclusion: higher titers of PLA2R-AB are related to worse kidney function outcome, higher 24-hour proteinuria, and a higher number of relapses in patients with pMN.

Key words: *membranous nephropathy, M-type phospholipase A2 receptor, autoantibodies, glomerulonephritis*

Introduction

Primary membranous nephropathy (MN) is an autoimmune glomerular disease characterized by the presence of autoantibodies to podocyte membrane

Correspondence to: *Mario Laganović, assistant professor, MD, PhD*, University Hospital Center Zagreb, Department for nephrology, arterial hypertension, dialysis and transplantation, Kišpatićeva 12, 10000 Zagreb
E-mail: mlaganovic@gmail.com

antigens and the formation of subepithelial immune complexes. Clinically it manifests as nephrotic syndrome and it is the most common cause of nephrotic syndrome in Caucasian adults[1-5]. Approximately one third of the patients enter spontaneous remission, and one third develop advanced chronic kidney disease, some of them requiring renal replacement therapy after 15 years[1,2,6]. In the last 10 years, significant progress was made in clarifying the etiopathogenesis of the disease. As major podocyte autoantigen, M-type phospholipase A2 receptor (PLA2R) was found, accounting for 50-80% of the cases of primary MN[7-9]. Other podocyte membrane autoantigens found so far in primary MN are thrombospondin type-1 domain-containing 7A (THSD7A)[10], neural epidermal growth factor-like 1 protein (NELL-1)[11], neutral endopeptidase (NEP)[12,] and exostosin1/exostosin2[13]. There are 2 routinely used methods for determining PLA2R autoantibodies (PLA2R-AB): indirect immunofluorescence (IIF), which is semiquantitative and more sensitive, and the ELISA method, which is quantitative and somewhat less sensitive[8,14,15]. There is still no consensus regarding the optimal cut-off values for positive findings, with the majority of studies using the cut-off value of 14-20 RU/ml in the ELISA test. There was a recent proposal for lowering the cut-off value to 2 RU/ml[16]. Numerous studies show the correlation between the titer of PLA2R-AB and the clinical course of the disease, but the true prognostic significance of the PLA2R-AB titer regarding kidney outcomes is still yet to be determined[4,8,16-18]. In this retrospective study, we have explored the correlation of PLA2R-AB status with clinical course and outcomes in patients with primary MN.

Patients and methods

The examined group consisted of 32 patients (21 males, 11 females), with a median age of 55.5 years (range 20 – 81 years) with renal biopsy and clinically proven pMN. Patients with a secondary form of MN were excluded from the study on a histological and clinical basis (negative serologic tests for lupus erythematosus and hepatitis, exclusion of malignancies depending on the age, etc.). During follow-up, all patients were treated according to KDIGO guidelines by the decision of the treating physician[19]. Outcomes were evaluated after 21 and 64 months of follow-up in 28 patients. The following variables were measured at the time of renal biopsy and during the follow-up visits: body proportions, blood pressure (BP), serum creatinine (SCr), estimated glomerular filtration rate (eGFR), 24h proteinuria (UP), serum albumin (SAlb) and PLA2R-AB (ELISA method, Euroimmun AG, Lübeck, Germany). Hypertension was considered blood pressure > 140/90 mmHg, increased serum creatinine as > 104 μmol/l, and stages of chronic kidney disease were defined after KDIGO guidelines[20], nephrotic proteinuria was defined as > 3.5 g/dU. According to the manufacturer, the ELISA results were considered positive at a level >20 RU/ml for IgG PLA2R-AB. Further categorization into groups was made according to PLA2R-AB levels: lower levels group (≤ 200 RU/ml) and higher levels group (> 200 RU/ml). Outcomes were defined as complete remission (24-hour proteinuria < 0.3g, normal SCr and eGFR), partial remission (24-hour proteinuria < 3.5g, or reduction for >50% from basal values, stable SCr or eGFR), no remission (unchanged or worsened initial parameters of renal function and proteinuria) and relapse (24-hour proteinuria > 3.5g and signs of nephrotic syndrome after achieving complete or partial remission).

Statistical analysis

Data are given as mean values+/-SDs or median values and ranges when appropriate. Patients were divided into two groups corresponding to the levels PLA2R-AB level at the start of the study (low and high). Differences in means between groups were assessed by Student's t-test. A c2 test or Fisher exact test was used for group comparisons regarding prevalence. Relationships between antiPLA2R-AB levels and clinical and laboratory parameters were examined by Pearson's correlation coefficient (r). Multivariant linear regression analysis was performed to quantify the strength of the association between antiPLA2R levels and several relevant variables. All results were considered statistically significant if $p < 0.05$. Statistical analysis was performed using STATISTICA, vers.8 (StatSoft., Inc).

Results

Clinical and laboratory characteristics of all subjects and regarding positivity of PLA2R-AB are shown in Table 1.

Table 1. Clinical and laboratory characteristics of all subjects and regarding positivity of PLA2R-AB

	Whole goup n=32			PLA2R-AB < 20 RU/ml n = 13			PLA2R-AB ≥ 20 RU/ml n = 19			*p*
Age (years)	53.7	±	13.5	57.0	±	15.2	51.5	±	12.2	0.269
Males (n/%)	21	/	65	9	/	69.2	12	/	63. 1	0.521
Serum creatinine (μmol/l)	114.7	±	58.1	116.1	±	76.5	99.2	±	34.9	0.081
eGFR (ml/min/1.73m^2)	72.3	±	31.3	65.2	±	36.5	77.5	±	26.8	0.286
24h proteinuria (g/dU)	7.92	±	4.36	7.08	±	4.68	8.53	±	4.15	0.371
Serum albumin (g/l)	28.8	±	6.4	31.1	±	5.5	27.2	±	6.7	0.126
PLA2R-AB (RU/ml)	138.1	±	268	2.1	±	1.3	231.3	±	318.3	**0.015**
Systolic BP (mmHg)	145.5	±	18.9	148.7	±	22.8	143.4	±	15.9	0.452
Diastolic BP (mmHg)	87.6	±	20.1	85.1	±	28.6	89.4	±	11.7	0.556
Time to remission (months)	7.9	±	4.4	8.8	±	5.4	7.4	±	3.9	0.497

Table 2. Clinical and laboratory characteristics of subjects regarding levels of PLA2R-AB

	PLA2R-AB < 200 RU/ml n = 11			PLA2R-AB ≥ 200 RU/ml n = 8			*p*
Age (years)	53	±	11.1	49.5	±	14.2	0.554
Males (n/%)	6	±	54.5	6	±	75.0	0.361
Serum creatinine (μmol/l)	96.7	±	33.5	103.1	±	39.3	0.715
eGFR (ml/min/1.73m^2)	77.2	±	25.8	78.1	±	30.5	0.945
24h proteinuria (g/dU)	8.41	±	4.32	8.72	±	4.21	0.881
Serum albumin (g/l)	28.4	±	7.1	24.7	±	5.4	0.311
PLA2R-AB (RU/ml)	61.9	±	31.8	464.2	±	389.9	**0.003**
Systolic BP (mmHg)	140.4	±	12.7	147.6	±	19.7	0.348
Diastolic BP (mmHg)	84.8	±	11.2	95.7	±	9.9	**0.041**
Time to remission (months)	7.4	±	3.9	7.5	±	4.6	0.967

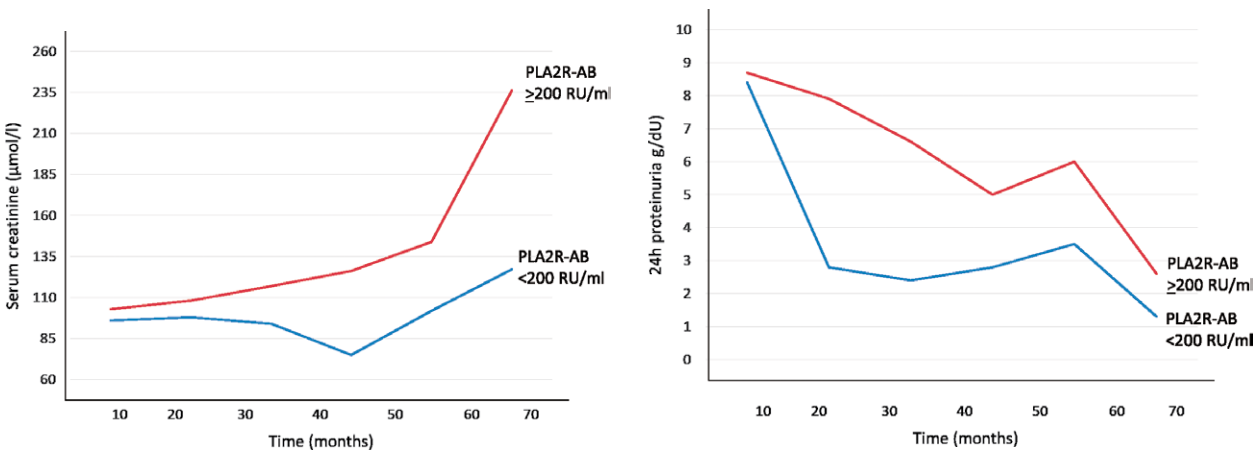

Figure 1. Outcome of renal function and proteinuria at the end of follow-up according to PLA2R-AB titer

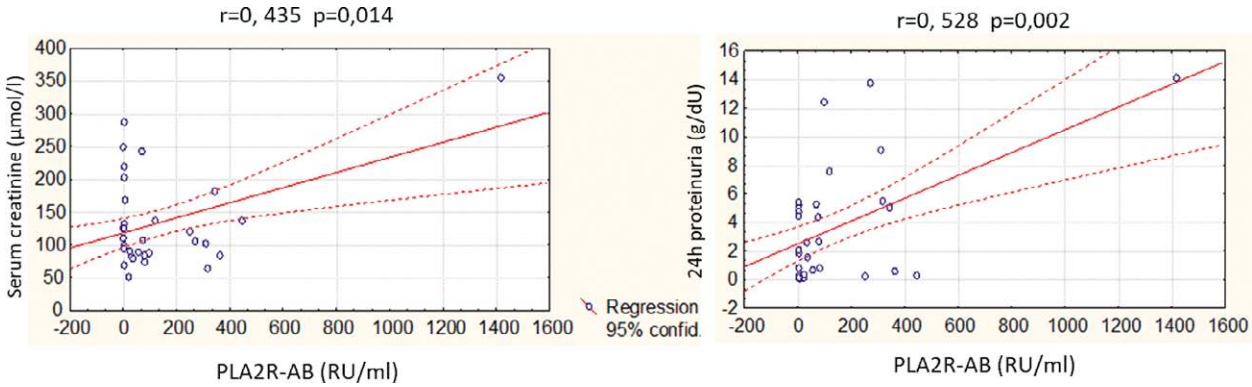

Figure 2. Correlation between PLA2R-AB titer and serum creatinine and 24-hour proteinuria after 21 months follow-up.

Table 3. Multivariant linear regression analysis of several variables on serum creatinine at the end of follow-up

	ß	SE	p
Systolic BP	-0.219	0.131	0.105
PLA2R- AB	0.527	0.124	<0.001
Serum creatinine (at the time of renal biopsy)	0.682	0.133	<0.001
24h proteinuria (at the time of renal biopsy)	0.110	0.126	0.391

Table 4. Multivariant linear regression analysis of several variables on 24h proteinuria at the end of follow-up

	ß	SE	p
Systolic BP	-0.207	0.169	0.232
PLA2R- AB	0.544	0.161	0.002
Serum creatinine (at the time of renal biopsy)	0.097	0.173	0.580
24h proteinuria (at the time of renal biopsy)	0.104	0.163	0.5299

Nineteen patients (59.3%) had positive PLA2R-AB (>20 RU/ml). There was no difference in basal values of BP, SCr, eGFR, 24-hour proteinuria, and SAlb according to negative or positive PLA2R-AB status. There were also no differences according to gender.

Clinical and laboratory characteristics of subjects regarding levels of PLA2R-AB are shown in table 2.

Patients with lower PLA2R-AB titer (<200 RU/ml) had significantly higher rates of remission after 21 months, compared to patients with higher PLA2R-AB titer (≥ 200 RU/ml) (90% vs. 50%, $\chi 2$ 4.0, p=0.045), and after 64 months the remission rate was still higher in low titer group, but the difference was not statistically significant anymore (80% vs. 50%, $\chi 2$ 1.57, p=0.210). The outcome of renal function and proteinuria at the end of follow-up according to PLA2R-AB titer is shown in figure 1.

The highest values of PLA2R-AB titer were found in patients without remission (88 vs. 265 RU/ml; p=0.093). 87% of patients with high PLA2R-AB titer had at least one relapse in 64 months vs. 63% in patients with low PLA2R-AB titer ($\chi 2$ 1.68, p=0.194). After 21 months, there were 71% of patients in remission and 63% after 64 months. There was a positive correlation between PLA2R-AB titer and SCr and PLA2R-AB titer and 24-hour proteinuria after 21 months (figure 2). Multivariant linear regression analysis found SCr and PLA2R-AB as significant predictors for kidney function at the end of follow-up (table 3). PLA2R-AB titer was an independent significant prognostic factor for 24-hour proteinuria at the end of follow-up (table 4).

Discussion

This study examined the temporal relationship between PLA2R-AB titer and clinical course in a cohort of Croatian primary MN patients. The incidence of PLA2R-AB in this study was 59.3%, comparable to the reported incidence of PLA2R-associated primary MN of 50-80%[8,9,14]. This variable incidence results from different cut-off values used, different timing re-

garding sampling in relation to the beginning of the disease, and different ethnicity. Lower incidences of around 50% are reported in Japanese patients[21]. We used the cut-off value of 20 RU/ml, which was used in the majority of studies and also recommended by the manufacturer, Euroimmun assay[15,18]. The diagnostic significance of PLA2R-AB has been confirmed and validated by numerous studies and generally is not disputed. Specificity and sensitivity of PLA2R-AB in differentiating between primary and secondary MN varies between studies, and a recent meta-analysis of 35 studies on 6085 patients by Li W et al., found the specificity of 97% and sensitivity of 65%[22]. There was no difference found in basal clinical characteristics between PLA2R-AB positive and negative patients, which is concordant with other studies, except that some studies found a correlation between 24-hour proteinuria at the beginning of the disease and PLA2R-AB titer, which we did not found[23]. The temporal association between PLA2R-AB status and clinical course of primary MN (mostly represented by 24-hour proteinuria) has also been well established[4,8,16-18]. Immunological activation of the disease precedes clinical signs for around 3 months[24]. Equally, clinical remission usually follows immunological remission by several months, as in spontaneous remission, as well as in therapy-induced remission[8,17,18,25]. Hence, most clinicians agree on the necessity of serial PLA2R-AB titer monitoring in primary MN patients[26]. The optimal interval for this is still yet to be determined, but it should be at least every 6 months. In most of the studies, there is a correlation between the PLA2R-AB titer and clinical outcomes of the disease. Spontaneous remission was more likely to occur in patients with a lower PLA2R-AB titer or with negative PLA2R-AB[27,28]. Reduction or disappearance of PLA2R-AB titer is associated with therapy-induced partial or complete remission in primary MN[18,29-38]. In our study, a significant difference was found in achieving remission at 21 months, regarding PLA2R-AB titer, but not after 64 months. Possible explanations for this finding include a smaller number of patients to achieve statistical significance and also a relapsing-remitting course of the disease, especially in long-duration follow-up. There are still some discrepancies regarding the prognostic significance of PLA2R-AB, which was also the main focus of our study. Primary MN typically is a slow progressive disease, and hard kidney endpoints (end-stage kidney disease ESKD; 50%-reduction in EGFR) are achieved after a long period of time. PLA2R-AB is known for about 10 years, and this interval is probably not long enough to have significant data on its prognostic value on hard kidney endpoints. Nonetheless, some studies have found that PLA2R-AB has prognostic significance. Mahmud M et al. found that a higher PLA2R-AB titer was associated with a higher risk of worsening kidney function (doubling serum creatinine)[39]. Similar was found by Qu Z et al.[30], Song EJ et al.[40] and Kanigicherla D. et al.[41]. On the contrary, Guo N et al.[31] didn't find PLA2R-AB titer as a significant predictor for kidney function during follow-up. A meta-analysis of 11 studies and 824 patients by Liang Y et al. found that PLA2R-AB titer was a significant predictor for the remission of the disease and renal failure, but not for the relapse of the disease[38]. In our study, we found PLA2R-AB, as well as serum creatinine as independent significant predictors for kidney function at the end of follow-up, and patients with higher PLA2R-AB titer had a greater risk for relapse. Also, we used a multivariable method to establish prognostic factors for kidney function, which is one of the strengths of our study.

Our study is limited by a relatively small number of patients, which lowers its statistical power. The retrospective nature of the study, different treatment schedules and not considering pathohistological findings represent other limitations to our study.

Nonetheless, this study is first in Croatian patients with primary membranous nephropathy to evaluate the status and prognostic significance of PLA2R-AB titer. Along with other published studies, it should contribute to better understanding the role of PLA2R-AB as a serologic marker in diagnosing the disease and also supporting its use in a personalized approach to prognosis and primary MN treatment.

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Sažetak

POVEZANOST PROTUTIJELA NA RECEPTOR ZA M-TIP FOSFOLIPAZU A2 S KLINIČKIM KARAKTERISTIKAMA I ISHODOM BOLESNIKA S PRIMARNOM MEMBRANSKOM NEFROPATIJOM U 5-GODIŠNJEM PRAĆENJU

M. Laganović, I. Horvatić, I. Bubić, M. Ilić, B. Maksimović, A. Kozmar, I. Vuković Brinar, M. Crnogorac, M. Živko, M. Fištrek, Ž. Jureković, D. Galešić Ljubanović, M. Ćorić, S. Bulimbašić, K. Galešić i *M. Knotek*

Uvod: primarna membranska nefropatija (pMN) je glomerulopatija, koja je u većini slučajeva uzrokovana autoprotutijelima na receptor za fosfolipazu A2 (PLA2R-PT). Cilj ovog istraživanja bio je analizirati povezanost PLA2R-PT s kliničkim tijekom i ishodima bolesti.

Ispitanici i metode: 32 bolesnika (21 muškaraca, 11 žena), s biopsijom bubrega dijagnosticiranim pMN, bilo je uključeno u istraživanje. PLA2R-PT (ELISA metoda) i ishodi (definirani u skladu s KDIGO) određeni su nakon 21 i 64 mjeseca praćenja u 28 bolesnika.

Rezultati: 19 bolesnika imalo je pozitivna PLA2R-PT (>20 RU/ml) (59.3%), s medijanom titra 97 (21-1418 RU/ml). Stopa remisije u skupini s niskim titrom PLA2R-PT (< 200 RU/ml) nakon 21 mjeseca bila je značajno viša u odnosu na skupinu s visokim titrom PLA2R-PT (≥ 200 RU/ml) (90% vs. 50%, p=0.045), a nakon 64 mjeseca razlika nije bila značajna (80% vs 50%, p=0.210). Stopa relapsa nakon 64 mjeseca bila je viša u skupini s visokim titrom PLA2R-PT (87% vs. 63%). Multivarijatnom linearnom regresijom su kao značajni neovisni prediktori za bubrežnu funkciju na kraju praćenja nađeni serumski kreatinin (ß=0.682, p<0.001) i PLA2R-PT (ß=0.527, p<0.001).

Zaključak: viši titar PLA2R-PT povezan je s lošijim ishodom bubrežne funkcije, višom 24-satnom proteinurijom i većom stopom relapsa u bolesnika s pMN.

Ključne riječi: *membranska nefropatija, protutijela na M-tip receptora za fosfolipazu A2, glomerulonefritis*