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Original Article

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Investigation of the Effect of THSD7A Level and PLA2R1 Polymorphism in Patients with Membranous Nephropathy

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ABSTRACT

Background: Membranous nephropathy (MN) is a glomerular disease characterized by subepithelial immune complex deposition and proteinuria. While phospholipase A2 receptor (PLA2R1) is the main autoantigen in idiopathic MN, thrombospondin type-1 domain-containing 7A (THSD7A) has also been implicated in a subset of patients. This study aims to evaluate the diagnostic and prognostic significance of serum THSD7A levels and PLA2R1 rs4664308 gene polymorphism in Turkish patients with MN.

Methods: Seventy biopsy-confirmed MN patients and 81 healthy controls were enrolled. Serum THSD7A levels were measured using enzyme-linked immunosorbent assay (ELISA), and rs4664308 genotyping was performed by TaqMan real-time polymerase chain reaction (PCR). Associations between THSD7A levels, genotypes, and clinical variables were analyzed using appropriate statistical methods. Receiver-operating characteristic (ROC) analysis was conducted to assess the diagnostic performance of THSD7A.

Results: Serum THSD7A levels were significantly higher in MN patients compared with controls ($P = .016$); however, ROC analysis demonstrated limited diagnostic value (area under the curve (AUC) = 0.671, sensitivity 70.6%, specificity 42.4%). The THSD7A levels showed no correlation with proteinuria, serum creatinine, estimated glomerular filtration rate, or blood pressure. The rs4664308 AA genotype and A allele were significantly more frequent in MN patients, whereas the AG genotype and G allele were more common in healthy controls ($P < .001$ and $P = .004$, respectively). No association was observed between rs4664308 genotypes and serum THSD7A concentrations.

Conclusion: Although serum THSD7A levels were elevated in MN patients, their limited diagnostic performance restricts their utility as standalone biomarkers. In contrast, the rs4664308 AA genotype and A allele were strongly associated with MN risk, suggesting potential value as genetic markers. Further studies are needed to confirm these findings and evaluate their prognostic significance.

Keywords: ELISA, genetic polymorphism, membranous nephropathy, PLA2R1, real-time PCR, rs4664308, THSD7A

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INTRODUCTION

Membranous nephropathy (MN), also known as membranous glomerulopathy, is one of the several glomerular diseases that lead to nephrotic syndrome. It is characterized by peripheral edema and proteinuria, often presenting as foamy urine. In MN, antigen-antibody complexes accumulate between the glomerular basement membrane and podocytes, activating the complement system and forming the membrane attack complex. This leads to disruption of podocyte structure and loss of the anionic charge barrier, resulting in proteinuria.[1]

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Membranous nephropathy is a chronic condition that occurs more frequently in men than in women. Spontaneous remission occurs in approximately 30% of patients, while those with persistent nephrotic syndrome are at high risk of progressing to end-stage kidney disease (ESKD).[2]

Primary (idiopathic) MN is considered an antibody-mediated autoimmune disease, although its pathogenesis is not fully understood. A significant advancement in understanding the disease came with the identification of 2 autoantigens: the M-type phospholipase A2 receptor (PLA2R) and thrombospondin type-1 domain-containing 7A (THSD7A). In 2009, Beck et al identified PLA2R1 as the major target antigen in idiopathic MN, with anti-PLA2R1 antibodies detected in 70% of affected individuals.[3] In 2014, Tomas et al discovered THSD7A antibodies in the sera of PLA2R1-negative idiopathic MN patients.[4] In addition to its role as an autoantibody target, THSD7A may be shed into the circulation as a consequence of podocyte injury. Podocyte detachment and membrane turnover can release extracellular fragments of transmembrane proteins, including PLA2R1 and THSD7A, into serum. Measuring circulating THSD7A antigen therefore provides insight into podocyte injury independent of antibody status.[5]

Conversely, higher autoantibody titers may promote formation and clearance of antigen–antibody complexes, decreasing the amount of detectable free antigen. These processes imply that circulating antigen levels may not correlate directly with antibody titers or clinical severity but may still reflect biologically relevant disease activity. Both PLA2R and THSD7A are high-molecular-weight, single-pass transmembrane proteins with multiple disulfide-rich extracellular domains.[6]

The presence of anti-PLA2R1 antibodies supports diagnosis in approximately 70% of patients, and genetic polymorphisms in the PLA2R1 gene have been associated with disease susceptibility. Three independent genome-wide association studies conducted in French (n = 75), Dutch (n = 146), and English (n = 335) cohorts identified rs4664308 as the strongest single nucleotide polymorphism (SNP) associated with idiopathic MN among 6 SNPs in the PLA2R1 gene located on chromosome 2.[7] A meta-analysis by Jing Yi Qiu et al, which included 6 studies, further confirmed the association of rs4664308 with idiopathic MN susceptibility across Asian, European, and Caucasian populations.[8]

Although PLA2R1 polymorphisms and THSD7A antibodies have been studied independently, there is a paucity of research investigating their combined impact on MN pathogenesis and prognosis. Identifying reliable biomarkers such as THSD7A levels or PLA2R1 genotypes could help predict disease progression, guide immunosuppressive treatment decisions, and improve individualized patient care. Whether the PLA2R1 rs4664308 polymorphism might be associated with variation in circulating THSD7A antigen levels was explored, acknowledging that these markers represent distinct biological pathways.

Given the notable ethnic differences reported in allele frequencies and genetic susceptibility patterns, evaluating these biomarkers in a Turkish cohort may provide valuable population-specific insights. Therefore, it was aimed to investigate whether the rs4664308 genotype influences serum THSD7A levels at the time of diagnosis and to assess the potential role of both markers as predictors of disease susceptibility or prognosis in membranous nephropathy.

MAIN POINTS

- This study evaluated the association between the phospholipase A2 receptor rs4664308 polymorphism and biopsy-proven membranous nephropathy in a Turkish population.
- The A allele and AA genotype of rs4664308 were more common in patients than in healthy controls, suggesting a genetic contribution to disease susceptibility.
- Serum thrombospondin type-1 domain-containing 7A concentrations were significantly higher in membranous nephropathy patients, but receiver operating characteristic analysis showed limited diagnostic performance.
- The findings highlight the role of genetic and serological markers in understanding disease mechanisms, although neither shows strong diagnostic accuracy alone.

MATERIALS AND METHODS

Study Group

Seventy adult patients with biopsy-proven membranous nephropathy who were evaluated at a tertiary care nephrology center were included in the study. Two blood samples were obtained from each patient at the time of enrollment: 5 mL collected in an ethylenediaminetetraacetic acid (EDTA) tube for deoxyribonucleic acid (DNA) extraction and 5 mL collected in a plain tube for serum separation. Clinicopathological data were retrieved from medical records. Clinical data (Proteinuria, Creatinine, eGFR, Hemoglobin (g/dl), Albumin(g/dl), Systolic and Diastolic blood pressure (mmHg)) were retrieved from medical records.

Eighty-one healthy individuals, unrelated to each other, with no known personal or familial history of kidney disease and aged between 18 and 70 years were included as the control group. A 5 mL peripheral blood sample collected in an EDTA tube was obtained from each control subject.

This genetic association study was designed and reported in accordance with the STREGA (Strengthening the Reporting of Genetic Association Studies) guidelines. The study was approved by İstanbul Faculty of Medicine ethics committee (Approval No: /206193; Date: 18.05.2021). Written informed consent was obtained from all participants. All procedures were conducted in accordance with the Declaration of Helsinki.

Measurement of Serum THSD7A Level and rs4664308 Genotyping

The blood samples were centrifuged right after collection. Sera were isolated from the blood samples in the dry tubes, DNA was isolated from the blood samples in the EDTA tubes, and they were kept at −20°C until the study time. The serum THSD7A concentrations were measured using quantitative enzyme-linked immunosorbent assay (ELISA) kits (Thermo Fisher Scientific, Waltham, MA, USA**).** The optimal cut-off for THSD7A was determined using Youden's index. rs4664308 genotyping was performed using the TaqMan SNP Genotyping (Thermo Fisher Scientific, Waltham, MA, USA) kit on a StepOnePlus Real-Time PCR System. rs4664308 was selected because it is the most widely studied PLA2R1 polymorphism associated with MN susceptibility in multiple populations.

Statistical Analysis

The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 30.0 (IBM SPSS Corp.; Armonk, NY, USA). Descriptive statistics were presented as appropriate. The normality of continuous variables was assessed using the Kolmogorov–Smirnov test.

Mean ± standard deviation values were used for the data that had normal distribution. The Pearson correlation test was used for correlation analyses between 2 numerical variables in the patient group. In the patient group, the data were compatible with the normal distribution and the Student's *t*-test was used for numerical comparisons between 2 groups. The 1-way ANOVA test was used for the data that were compatible with the normal distribution and for numerical comparisons among more than 2 groups. Receiver-operating characteristic (ROC) analysis was performed to specify the cut-off value, sensitivity, and specificity for the ELISA results. The *chi*-square test was used for the categorical data. The results were expressed as percentage values. A *P* value of <.05 was considered statistically significant. Hardy–Weinberg equilibrium was assessed for the rs4664308 genotypes in both cases and controls. No missing genotype data were observed for rs4664308.

RESULTS

In the patient group, the mean age was found to be 55.57 ± 14.26 years and the mean age at the time of diagnosis was found to be 48.49 ± 14.14 years. Both current age and age at diagnosis were included in the analysis, as they represent distinct clinical variables. Thirty-four of the patients were male (48.6%, 55.06 ± 12.8) and 36 were female (51.4%, 56.09 ± 15.7). The patients were followed up for a mean period of 87.75 ± 29.3 months after the diagnosis was made. Among the 81 healthy individuals included in the study, 42 were male (51.9%, 47.48 ± 12.1), 39 were female (48.1%, 48.49 ± 16.6) and the mean age was 47.96 ± 14.3 years. When the patient and control groups were evaluated in terms of sex, a statistical significance was not observed (*P* = .688).

Serum THSD7A Level

A statistical significance was not found between serum THSD7A level and age, proteinuria, follow-up proteinuria, creatinine, hemoglobin, and systolic and diastolic blood pressure (BP). Although estimated glomerular filtration rate (eGFR) showed a negative correlation with hemoglobin and albumin, a statistical significance was not found (*P* > .05) (Table 1). A significant relationship was not found between THSD7A level and remission, development of ESKD, genotype and medical treatment (ACEI-Angiotensin converting enzyme inhibitor or ARB-Angiotensin II Receptor Blocker) (*P* > .05).

The ROC curve analysis was performed to measure the area under the curve (AUC) value for THSD7A. The AUC value for THSD7A was found to be 0.671 (95% CI: 0.542-0.799) (*P* = .016). The best cut-off value for THSD7A to predict disease progression was considered 1.522 pg/mL (sensitivity: 70.6%, specificity: 42.4%) (Figure 1). The patients were divided into 2 groups as group 1 (patients who had values below this cut-off) and group 2 (patients who had values above this cut-off). The relationship between clinical parameters were investigated to evaluate if THSD7A was associated with disease severity (Table 2).

rs4664308 Genotype

The AA genotype was found to be significant in the patients compared to the control group (*P* = .001). The AG genotype was found to be significant in the control group (*P* = .001). The A allele was found to be significant in the patient group and the G allele was found to be significant in healthy controls (*P* = .004) (Table 3).

In all rs4664308 genotypes, statistical significance was not found between serum THSD7A level and sex, age, serum creatinine, proteinuria, proteinuria after follow-up, and eGFR (*P* > .05). The association between rs4664308 genotype and serum THSD7A level groups defined according to the ROC-derived

Table 1. Correlation Between Serum THSD7A Levels and Clinical Parameters in Patients with Membranous Nephropathy

Clinical Parameters	n	*P*	*r*
Age	70	.675	0.052
	62	.695	0.051
	59	.773	0.038
	67	.852	0.023
	67	.254	0.141
	65	.633	0.060
	70	.488	0.084
	49	.313	0.021
	49	.134	0.180

BP, blood pressure; eGFR, estimated glomerular filtration rate.

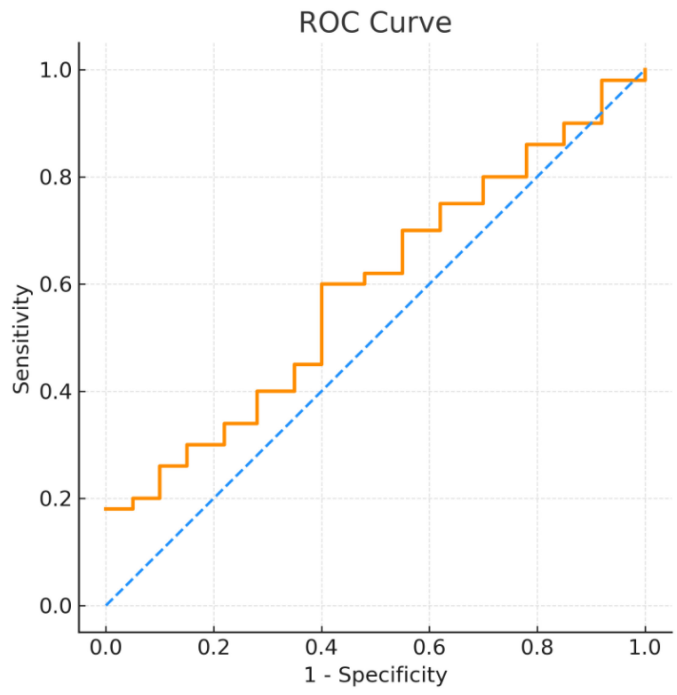

Figure 1. ROC curve of serum THSD7A levels in patients with membranous nephropathy. The curve illustrates the diagnostic performance of circulating THSD7A antigen levels. The 95% CI for the AUC and optimal threshold were calculated using Youden's index.

Table 2. Comparison of Clinical Parameters Between Group 1 and Group 2 Based on ROC-Derived THSD7A Cut-Off

Parameter	Group 1 (n = 30)	Group 2 (n = 40)	*P*
Age (years)	56.97 ± 12.23	54.54 ± 15.68	.492
Gender (M/F)	17 / 13	19 / 21	.448
Age at diagnosis (years)	49.28 ± 12.65	47.90 ± 15.29	.694
Weight (kg)	76.50 ± 12.90	78.00 ± 15.58	.719
Systolic BP (mmHg)	128.48 ± 16.48	135.00 ± 17.49	.187
Diastolic BP (mmHg)	77.61 ± 10.86	82.88 ± 10.97	.098
Serum albumin (g/dL)	2.69 ± 0.81	2.64 ± 1.13	.847
Serum creatinine (mg/dL)	0.86 ± 0.58	0.87 ± 0.37	.989
Hemoglobin (g/dL)	12.82 ± 1.97	12.76 ± 2.06	.911
eGFR (mL/min/1.73 m^2)	109.38 ± 49.24	99.56 ± 57.08	.462
Proteinuria (mg/day)	5407.73 ± 3095.08	5469.61 ± 3232.68	.940
Proteinuria at follow-up (mg/day)	2923.12 ± 2601.46	2621.64 ± 2405.47	.646

BP, blood pressure; eGFR, estimated glomerular filtration rate.

Table 3. Distribution of PLA2R1 rs4664308 Genotypes and Alleles in Membranous Nephropathy Patients and Healthy Controls

	Patient Group	Control Group	*P*
Genotype	n:70 (%)	n:81 (%)	
AA	56 (80)	44 (54)	***.001***
AG	14 (20)	37 (46)	
Allele	n:140	n:162	
A	126	125	***.004***
G	14	37	

cut-off (below vs. above cut-off) was evaluated. The distribution of rs4664308 genotypes did not differ significantly between the 2 serum THSD7A groups ($P > .206$).

DISCUSSION

Membranous nephropathy is a chronic autoimmune glomerular disease characterized by subepithelial immune complex deposition, complement activation, and progressive podocyte injury. The condition occurs predominantly in adults and tends to progress more rapidly in older individuals and in men, although demographic influences vary substantially across cohorts.[3,4,9,10] In the cohort, however, no significant associations were observed between sex, age, and disease severity, which may be attributable to the limited number of patients in advanced stages of MN.

Beyond these demographic patterns, increasing attention has been directed toward molecular biomarkers that may account for the clinical heterogeneity of MN and refine prognostic assessment. Among these markers, THSD7A represents a pathogenic antigen in a minority subset of patients, yet published studies have reported inconsistent relationships between THSD7A status and clinical severity, suggesting considerable biological variability across MN phenotypes. Against this background, the performance of circulating THSD7A antigen levels in the cohort was evaluated. In the study, serum THSD7A levels were higher in MN patients, but this increase did not correlate with clinical parameters such as proteinuria, serum creatinine, albumin, or eGFR. Similar to the findings, previous studies have reported that THSD7A antigen or antibody levels do not consistently associate with proteinuria or kidneyfunction.[11,12] Although the ROC analysis yielded a statistically significant AUC of 0.671, this value indicates limited discriminatory capacity, consistent with biomarker literature classifying AUC values of 0.60-0.70 as poor diagnostic performance.[13] Moreover, THSD7A-positive MN represents only a small subset of cases, which inherently limits its standalone diagnostic potential.[4,14] The absence of strong associations in the cohort may reflect small effect sizes, sample size limitations, or heterogeneity in disease stage and treatment status at the time of sampling. Nevertheless, reporting weak or negative findings is important to avoid overinterpretation of THSD7A assays and underscores the need for multimarker panels rather than reliance on a single circulating antigen.

The absence of a strong relationship between circulating THSD7A antigen and disease severity may also be explained by competing biological mechanisms. Podocyte injury can promote proteolytic shedding of THSD7A and PLA2R, releasing antigenic fragments into the extracellular space.[5] Conversely, high autoantibody titers may facilitate immune complex formation, thereby reducing measurable free antigen despite ongoing disease activity.[15] Similar observations have been reported for other MN-associated antigens, where antibody titers do not consistently correlate with clinical activity.[16]

The PLA2R1 gene plays a central role in MN pathogenesis through genetic susceptibility mechanisms. Eight distinct C-type lectin domains of the PLA2R1 transmembrane protein can bind anti-PLA2R1 antibodies, and epitopes within these domains may participate in autoantibody generation. The PLA2R1 gene, located on chromosome 2q23–q24, contains multiple SNP regions, among which rs4664308 has been the most consistently associated with idiopathic MN.[17,18] Studies conducted in India, China, Spain, France, the United Kingdom, and the Netherlands have demonstrated that both the prevalence of MN and the distribution of PLA2R1 polymorphisms vary across ethnic groups.[19] A meta-analysis including 9 studies reported that the minor G allele of rs4664308 may confer protection against idiopathic MN.[20] In the study, genotype frequencies did not differ by age, suggesting that age was not a confounding factor in genetic comparisons. However, the A allele and AA genotype were significantly more common in MN patients than in healthy controls. No associations were observed between rs4664308 and clinical parameters such as THSD7A level, proteinuria, follow-up proteinuria, creatinine, or eGFR.

Although the rs4664308 polymorphism and circulating THSD7A antigen levels represent distinct biological domains—genetic susceptibility and podocyte antigen shedding—they converge on the same autoimmune process underlying membranous nephropathy. Evaluating these markers within the same cohort therefore provides complementary information rather than a direct mechanistic linkage. The lack of association between genotype and THSD7A level suggests that rs4664308 does not influence antigen shedding dynamics.

This study has several limitations. The sample size was relatively small, which may have reduced the statistical power to detect associations, particularly for THSD7A. Additionally, only a single time-point measurement was available for THSD7A, preventing evaluation of disease activity trends over time. Anti-THSD7A and anti-PLA2R antibody titers were not measured, limiting the ability to explore antigen–antibody dynamics directly. Future studies with larger, multiethnic cohorts and longitudinal biomarker measurements are warranted to clarify the prognostic value of these markers.

In this study, whether circulating THSD7A antigen levels and the PLA2R1 rs4664308 polymorphism could serve as biomarkers for membranous nephropathy was investigated. Although THSD7A levels were higher in MN patients, they did not correlate with clinical or laboratory indicators of disease severity, suggesting that THSD7A alone lacks sufficient discriminatory value as a diagnostic or prognostic marker. In contrast, the PLA2R1 rs4664308 AA genotype and A allele were significantly associated with MN susceptibility in the cohort, whereas the AG genotype appeared protective, supporting the relevance of population-specific genetic risk profiles. These findings highlight the importance of integrating genetic markers into MN research, while also demonstrating the limited clinical utility of circulating THSD7A antigen levels at the time of diagnosis. Larger and longitudinal studies incorporating both antigen and antibody measurements are warranted to further elucidate the combined roles of genetic variants and podocyte antigens in MN pathogenesis and disease monitoring.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Artificial Intelligence Usage Statement: The authors declared that no Artificial Intelligence Tool was used in the preparation of the manuscript.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of İstanbul University Faculty of Medicine (Approval no: 206193, Date: 18.05.2021).

Informed Consent: Written informed consent was obtained from participants who agreed to take part in the study.

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Declaration of Interests: The authors have no conflict of interest to declare.

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