



Phospholipase A2 receptor is associated with hypercoagulable status in membranous nephropathy: a narrative review

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Background and Objective: Membranous nephropathy (MN) is the pathology type with the highest incidence of thrombotic events in nephrotic syndrome (NS). While patients with MN are prone to developing thromboembolic complications, the specific mechanism remains unclear. Many studies have shown a high titer of PLA2R antibody aggravates proteinuria and hypoalbuminemia and predicts a lower likelihood of clinical remission in patients with PLA2R-associated MN. Proteinuria and hypoalbuminemia also increase the risk of thrombotic events. In our previous review, we found secretory phospholipase A2 (sPLA2) may act as a ligand for PLA2R, and binding of sPLA2 to PLA2R results in damage to podocytes. sPLA2 can promote the release of AA from membrane phospholipids, and AA is closely related to blood lipid levels and coagulation cascades. The objective of this study is to explain the relationship between phospholipase A2 receptor (PLA2R) and blood hypercoagulability in MN patients and the new theory that secretory phospholipase A2 (sPLA2) and arachidonic acid (AA) may play a role in regulating blood lipid levels and the coagulation cascade in patients with PLA2R-positive MN.

Methods: Literature retrieval was conducted through China National Knowledge Infrastructure (CNKI) and PubMed. Abstract and Introduction information was then retrieved and the results from the literature searched, classified, and important information summarized. A conclusion was then reached, and a new standpoint put forward.

Key Content and Findings: We discussed the role of PLA2R antibody and sPLA2 in hypercoagulability in patients with MN and analyzed the following four possible mechanisms: sPLA2 can combine with PLA2R and induce podocyte apoptosis; sPLA2 may promote the production of anti-PLA2R antibodies; sPLA2 may promote the release of AA from membrane phospholipids; and AA induces platelet aggregation.

Conclusions: PLA2R may exacerbate hypercoagulability in patients with PLA2R-related MN, and sPLA2 plays an important role in the process.

Keywords: Arachidonic acid (AA); coagulation disorder; membranous nephropathy (MN); phospholipase A2 receptor (PLA2R); secretory phospholipase A2 (sPLA2)

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Introduction

Membranous nephropathy (MN) is the most common cause of adult nephrotic syndrome (NS). The clinical manifestations of MN include massive proteinuria, hypoalbuminemia, prominent edema, and hyperlipidemia, and there are two manifestations: primary and secondary forms. In 25% of patients, the occurrence of MN is associated with underlying disease such as systemic lupus erythematosus and malignant tumor, exposure to certain drugs, or infection (viral, bacterial). Primary MN is diagnosed if no secondary cause is apparent (1). The main pathophysiology of MN consists of the deposition of immune complexes at the bottom of podocyte foot processes (2). Recent discovery of the phospholipase A2 receptor (PLA2R) represents a significant medical advance in our understanding of MN, as its presence serves as a basis for differentiating primary and secondary forms of the disease. However, coagulation cascade disturbances in patients with MN remain to be fully elucidated. Many studies (3-8) have shown that a high titer of PLA2R antibody aggravates proteinuria and hypoalbuminemia and predicts a lower likelihood of clinical remission in patients with PLA2R-associated MN. Factors such as proteinuria and hypoalbuminemia also increase the risk of thrombotic events. A study has shown that secretory phospholipase A2 (sPLA2) can promote the release of arachidonic acid (AA) from membrane phospholipids and serves as a high-affinity ligand for PLA2R (9). Furthermore, AA exhibits a close association with lipid metabolism and the coagulation process. Most of the previous studies focused on proteinuria and hypoalbuminemia, and there were few studies on the specific mechanism. In this review, we analyze the relationship between PLA2R and blood hypercoagulability in MN patients and discuss the potential role of sPLA2 in the disturbance of coagulation cascades in patients with PLA2R-related MN. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-3572/rc>).

Methods

China National Knowledge Infrastructure (CNKI) and PubMed searches were performed using the key words “arachidonic acid”, “coagulation disorder”, “membranous nephropathy”, “PLA2R”, and “sPLA2” to identify relevant articles published in multiple languages and fields. We

searched all types of relevant literature from 1991 to 2021, many related literatures were retrieved and abstract and introduction information was retrieved. After familiarizing ourselves with the research status at home and abroad, we formulated preliminary research ideas and further screened and consulted literatures. Ultimately, 47 relevant articles were selected. We classified and summarized important information before drawing our own conclusions and offering a new standpoint (*Table 1*).

Discussion

The main complications of NS include infection, thromboembolic disease, acute kidney injury and protein metabolism disorder. Venous thromboembolism (VTE) is a common and serious complication of NS and includes deep vein thrombosis (DVT), renal vein thrombosis (RVT), and pulmonary embolism (PE). MN is the most common type of NS with thromboembolism (10), in which the incidence of RVT can be as high as 40% to 50% (10). While the process responsible for the hypercoagulable state in patients with MN remains to be elucidated, recent study has shown that syndecan-1 (SDC-1) may be associated with hypercoagulability and thromboembolism in patients with the disease (11).

PLA2R antibody has high specificity and sensitivity. In patients with PLA2R antibody associated IMN, serum PLA2R antibody level and PLA2R expression in kidney tissue were significantly increased (12). A study (13) has shown that the serum positive rate of PLA2R antibody in IMN patients is 70–80%. Other study (14) has shown that PLA2R can be continuously expressed in protocellular cells, and the expression of PLA2R can be detected in renal tissues of about 75% IMN patients. Multiple studies (15,16) have confirmed that the expression of PLA2R in renal tissue is expressed on protocellular surface through intracellular recycling, and is not affected by changes in patients' conditions, so its diagnosis of IMN has a high stability. Studies (17,18) have shown that the risk of renal function progression increases with the increase of PLA2R antibody levels. Therefore, PLA2R is closely related to the diagnosis, treatment, occurrence and development of IMN.

However, the relationship between PLA2R and hypercoagulability in MN remains unclear. Current research suggests that with the loss and compensatory increase in the synthesis of urinary protein, changes in a variety of coagulation factors and associated regulators involved in coagulation and fibrinolysis occur, and in

Table 1 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	2021.05.01–2021.07.01
Databases and other sources searched	CNKI, PubMed
Search terms used (including MeSH and free text search terms and filters)	Arachidonic acid, coagulation disorder, membranous nephropathy, phospholipase A2 receptor, secretory phospholipase A2
Timeframe	1991–2021
Inclusion and exclusion criteria (study type, language restrictions etc.)	All types of articles were included in the analysis
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	All authors refer to relevant articles, and those with different opinions focus on discussion

Table 2 Association of PLA2R-ab titer with proteinuria (Alb) in patients with PLA2R-related MN

Author	Study design	Biochemical indicators	N: outcome
Antonella Radice <i>et al.</i> (3)	Prospective study in patients with PLA2R-related MN	Proteinuria; Alb; PLA2R-ab titer	42: the positive PLA2R serum antibody status was linearly associated with increasing proteinuria and decreasing serum albumin over time, compared with negative antibody status
Zhang Qiuhua <i>et al.</i> (4)	Prospective study in patients with PLA2R-related MN	Proteinuria; Alb; PLA2R-ab titer	552: patients with high serum PLA2R-ab drops had significantly lower Alb (30.93 vs. 35.80 g/L, $P=0.048$) and higher 24-hour proteinuria (2.34 vs. 1.22 g/day, $P=0.031$) than those with low titers
Qu Zhen <i>et al.</i> (5)	Prospective study in patients with PLA2R-related MN	Proteinuria; Alb; PLA2R-ab titer	359: the level of PLA2R-ab was positively correlated with urine protein ($r=0.164$, $P=0.002$) and negatively correlated with Alb ($r=-0.229$, $P<0.001$)
Elion Hoxha <i>et al.</i> (6)	Prospective study in patients with PLA2R-related MN	Proteinuria; Alb; PLA2R-ab titer	133: the decrease of serum PLA2R-ab level is associated with the decrease of proteinuria and the increase of Alb
Han Wenwen <i>et al.</i> (7)	Prospective study in patients with PLA2R-related MN	Proteinuria; PLA2R-ab titer	56: there was a significant positive correlation between PLA2R-ab titer and proteinuria during treatment
Jyun Ni Chi <i>et al.</i> (8)	Prospective study in patients with PLA2R-related MN	Proteinuria; PLA2R-ab titer	72: the titer of PLA2R-ab antibody was positively correlated with the severity of proteinuria ($r=0.3227$, $P=0.03$)

PLA2R, phospholipase A2 receptor; ab, antibody; Alb, serum albumin; MN, membranous nephropathy.

combination, these changes contribute to a prothrombotic environment (10). Other pathological characteristics of MN, in combination with the concomitant use of diuretics and immunosuppressive agents, may further increase the risk of thrombosis in these patients.

PLA2R antibody binds to podocyte PLA2R antigens, leading to the formation of membrane attack complexes that include podocytes, resulting in cytotoxicity with filtration barrier disruption and the development of proteinuria. Many studies (3–8) indicated PLA2R antibody titers were positively correlated with proteinuric levels and negatively correlated with serum albumin (Table 2). Serum albumin is

an important determinant that assists in evaluating whether patients with MN need anticoagulation. Those with a high PLA2R antibody titer frequently have lower serum albumin, placing them at a greater risk of thrombotic events than those with negative PLA2R antibody or those with a low antibody titer. Other studies (4,19–23) showed spontaneous remission rates were lower among PLA2R antibody positive patients than those with a negative PLA2R (Table 3). A meta-analysis (24) of 2,345 patients from 29 cohorts showed difficulty in achieving remission is synonymous with a more severe and protracted course of proteinuria and hypoalbuminemia, placing patients at an increased risk of

Table 3 Association between PLA2R-ab titer and remission

Author	Study design	Cutoff value, N	Outcome
Zhang Qiuhoa <i>et al.</i> (4)	Prospective study in patients with PLA2R-related MN	0.91 mg/L, 552	The clinical remission rate (51.22 vs. 82.35%, $P=0.027$) and complete remission rate (47.62% vs. 64.29%) in patients with high titer were also significantly lower than those with low titer
Sjoerd A. M. E. G. Timmermans <i>et al.</i> (19)	Prospective study in patients with PLA2R-related MN	2 RU/mL, 73	Patients with low PLA2R-ab had the highest rate of spontaneous remission (79%)
Piero Ruggenenti <i>et al.</i> (20)	Prospective study in patients with PLA2R-related MN	14 RU/mL, 154	Lower PLA2R-ab titers strongly predicted higher remission rates and shorter remission times. After initial reduction or complete depletion, PLA2R-ab titers increase after initial reduction or complete depletion, strongly indicating recurrence of the disease
Franck Pourcine <i>et al.</i> (21)	Retrospective study in patients with PLA2R-related MN	14 RU/mL, 108	Patients who had cleared PLA2R-ab from serum within 6 months had a greater chance of clinical remission than those who remained serologically positive
Elion Hoxha <i>et al.</i> (22)	Prospective study in patients with PLA2R-related MN	14 RU/mL, 37	Patients with PLA2R-ab negative MN had high rates of spontaneous proteinuria remission
Dan Dong <i>et al.</i> (23)	A meta-analysis about PLA2R-related MN	N=1,642	Remission rate in the serum anti-PLA2R antibody-positive group was lower than that in the -negative group (OR =0.41, 95% CI: 0.28, 0.61, $P<0.00001$)

PLA2R, phospholipase A2 receptor; ab, antibody; MN, membranous nephropathy.

thrombosis. In addition, we found in a literature review that PLA2R may further aggravate blood hypercoagulation in MN patients through sPLA2 and AA pathways. Therefore, it is important to elucidate the risk and associated mechanism responsible for thrombotic events in patients with PLA2R-associated MN.

sPLA2 has been shown to serve as a high-affinity ligand for PLA2R, promoting the release of AA from membrane phospholipids in mice (25). AA has been linked to lipid metabolism and blood clotting, and below, we propose potential roles for sPLA2 and AA in coagulation disorders among patients with PLA2R-related MN.

sPLA2, in combination with PLA2R, induces podocyte apoptosis

sPLA2 is a ligand with high affinity for PLA2R (25), which regulates multiple biological effects of the former. sPLA2-IB, an endogenous PLA2R ligand, induces cell proliferation, as well as the migration and production of lipid mediators (26). Using a mouse model, Beck *et al.* (27) found the expression of sPLA2-IB and its receptor in the kidney increased significantly. Another study (21) of 245 patients showed the level of circulating sPLA2-IB in idiopathic and secondary MN was significantly higher than

in the control group, and sPLA2-IB levels were negatively correlated with serum albumin while positively correlated with 24-hour urinary protein amount. The role of sPLA2-IB in the diagnosis of both idiopathic and secondary MN remained undetermined in their study, but others (28) showed podocytes transfected with a PLA2R plasmid exhibited higher levels of apoptosis in response to sPLA2-IB treatment. These findings suggest sPLA2-IB may induce human podocyte apoptosis by binding with PLA2R. The sPLA2-IB-PLA2R interaction stimulates podocyte apoptosis by activating ERK1/2 and cPLA2 and increasing podocyte AA content. In patients with MN, the apoptosis rate of podocytes increased in groups with higher PLA2R expression and increased serum sPLA2-IB levels, while groups with higher PLA2R expression had lower serum albumin levels and higher urine protein levels (28). The pathogenesis of PLA2R-related MN mainly consists of three steps: the formation of PLA2R antigen-antibody immune complexes activate the complement system, allowing membrane attack complexes to enter cells, resulting in cellular toxicity and destroying the filtration barrier. Finally, patients develop proteinuria. sPLA2-IB may induce podocyte apoptosis by binding with PLA2R, further increasing proteinuria and exacerbating hypoalbuminemia in patients with MN. Abnormal platelet activation and aggregation in patients

with NS may also increase platelet counts and promote the release of active substances. As albumin inhibits the production and release of AA and thromboxane A₂ (TXA₂), hypoalbuminemia in patients with NS increases their platelet count, while the activation and aggregation of platelets (29) exacerbates coagulation disorders and hypercoagulability in patients with PLA2R-related MN.

sPLA2 may promote the production of anti-PLA2R antibodies

A new study indicates the percentage of circulating plasma cells and regulatory B cells (Breg) in patients with MN is significantly higher than patients with non-immune-mediated chronic kidney disease and healthy controls (30). Anti-PLA2R antibodies are typically of the IgG4 subtype (1), and the production of IgG4 in patients with MN requires prior antigen presentation to CD4⁺ T-cells, which transform into corresponding T-helper cells 2 (Th2). Th2 cells and their secreted cytokines, including interleukin-4 (IL-4), IL-5, IL-6, and IL-10, activate B lymphocytes and generate specific IgG4 (31-33). In addition to enzymatic hydrolysis, sPLA2 has many effects, including the induction of cell proliferation, migration, hormone release, the production of lipid mediators, and cytokines, and relevant signal transduction. These effects are generated after sPLA2 binds to PLA2R. In the kidney, sPLA2 increases the expressions of PLA2R antigens by upregulating PLA2R expression (28), and this facilitates antigen presentation and increases the production of anti-PLA2R antibody. In addition, AA metabolism can produce many factors that regulate lipids, such as prostaglandin, thromboxane, interleukin, and lipoxigenin (34,35). Previous study has shown sPLA2 can activate cytokines such as tumor necrosis factor (TNF), IL-1, and IL-6 (36), which promote B-cell activation and increase antibody production, while other studies (7,12,37) also showed levels of serum PLA2R were proportional to those of urine protein antibody. Thus, by increasing the production of anti-PLA2R antibodies, sPLA2 exacerbates hypoproteinemia, further stimulating the activation and aggregation of platelets, leading to coagulation disturbance and, ultimately, to blood hypercoagulability in patients with PLA2R-related MN.

sPLA2 may promote the release of AA from membrane phospholipids

sPLA2 is a phospholipid polymerase and a ligand that

can affect cellular survival. sPLA2 belongs to the PLA2 superfamily of enzymes, which catalyze the hydrolysis of sn2 ester bonds in glycerolipid, releasing free fatty acids and hemolytic lecithin (38). Therefore, AA-containing phospholipids can be hydrolyzed by PLA2, producing free AA and hemolytic lecithin (9). In the kidney, sPLA2-IB stimulates cPLA2a phosphorylation in podocytes through activation of the ERK1/2 pathway and increases AA production by upregulating PLA2R (28).

AA induces platelet aggregation

Vascular obstruction related to thrombosis is often due to uncontrolled platelet over-activation, leading to platelet dysfunction (39,40). Platelets are the smallest type of blood cells and play an important role in blood circulation, vascular integrity, and hemostasis (41). Excessive systemic platelet aggregation leads to thrombus formation and even acute coronary syndrome (ACS) (42). AA is a precursor of thrombin and prostacyclin compounds that is capable of regulating platelet function (43). Platelet aggregation is mediated by the synthesis of prostaglandin G₂, prostaglandin H₂, and TXA₂, which are derived from the catalytic effects of cyclooxygenase (COX) on AA released from platelet membranes. These aggregates lead to increased intracellular Ca²⁺ mobilization through the inhibition of nitric oxide (NO) synthesis. Ca²⁺ released from dense granules in platelet cytoplasm can activate sPLA2, releasing AA from platelet membrane phospholipids (44). AA produces TXA₂ (45) under the action of COX-1 and TXA synthase, leading to greater platelet aggregation. A study has shown complement C5B-9 damages glomerular epithelial cells by releasing AA, further aggravating hypoalbuminemia and hypercoagulability (46).

Conclusions

In summary, the discovery of PLA2R and its pathogenic role is an important milestone in the study of MN. Previous studies have clarified the pathogenesis, diagnosis, treatment, and prognosis of patients with PLA2R-related MN, but few have addressed the origin of the hypercoagulable state and the disturbed coagulation cascade. As a high-affinity ligand for PLA2R, sPLA2 plays an important role in complications associated with MN, and the serum titer of anti-PLA2R increases in patients with PLA2R-related MN. Based on the three lines of evidence outlined above, we infer sPLA2 may promote hypercoagulability in patients with PLA2R-related

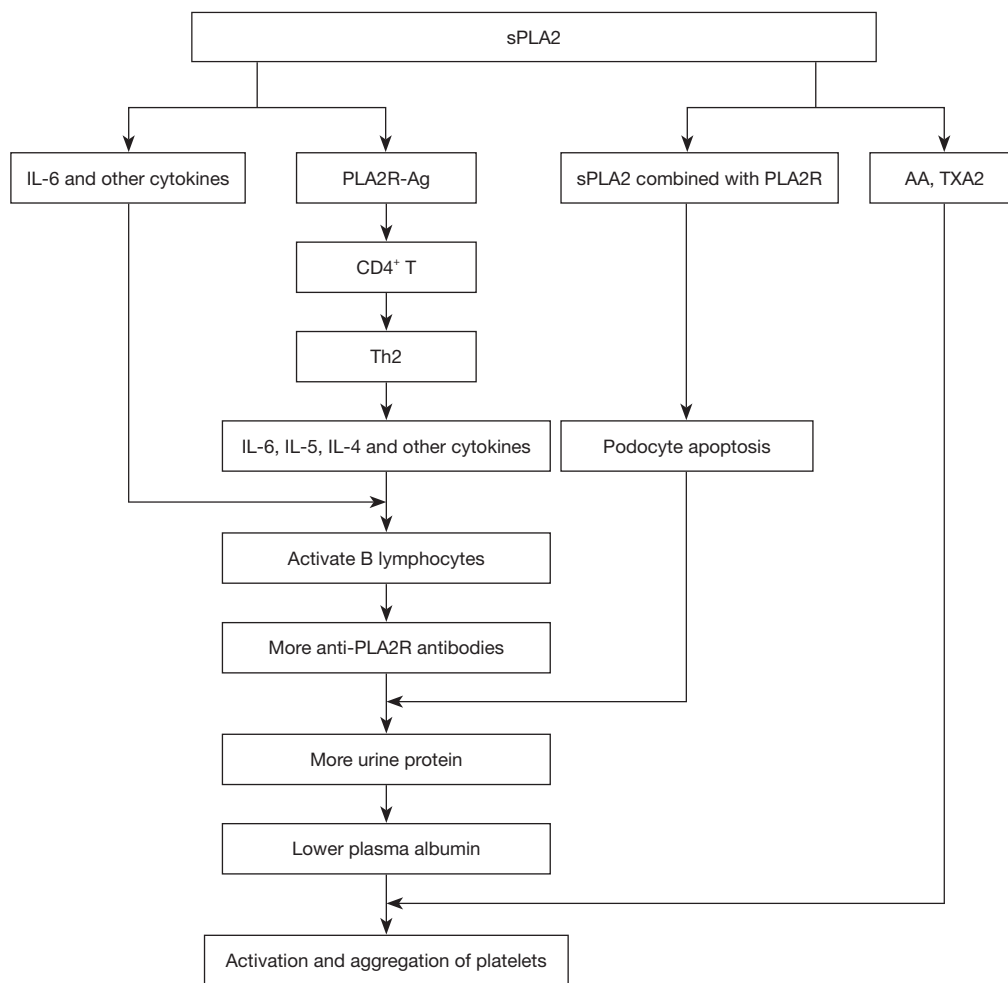


Figure 1 Potential mechanisms responsible for coagulation disorders in patients with PLA2R-related membranous nephropathy. sPLA2, secretory phospholipase A2; PLA2R, phospholipase A2 receptor; IL, interleukin; AA, arachidonic acid.

MN (Figure 1). The limitation of this finding is the lack of data support, and we are conducting a prospective study to explore this mechanism. At the same time, additional studies are required to elucidate the mechanisms responsible for the disturbed coagulation cascades in patients with PLA2R-related MN.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-3572/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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