

A new non-invasive approach using urinary AIT-EVs for the diagnosis of membranous nephropathy

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Received: January 5, 2026; Accepted: September 4, 2026; Published Online: September 5, 2026; <https://doi.org/10.59717/j.xinn-med.2027.100277>

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Citation: Qi E. and Li X. (2027). A new non-invasive approach using urinary AIT-EVs for the diagnosis of membranous nephropathy. *The Innovation Medicine* 5:100277.

INTRODUCTION

As a common cause of nephrotic syndrome in adults, membranous nephropathy (MN) has long been defined as a pattern of injury mediated by the binding of autoantibodies to specific target antigens, characterized by the accumulation of immune complexes containing immunoglobulin G (IgG) and target antigens in the subepithelial region of the glomerular basement membrane (GBM).¹ Over the past two decades, the successive discovery of multiple target antigens has greatly advanced our understanding of MN. Notably, the identification of anti-phospholipase A2 receptor (PLA2R) antibodies by Beck Jr et al. in 2009 directly validated the concept that circulating autoantibodies can target endogenous podocyte antigens.² Nowadays, PLA2R testing is widely used for diagnosis and monitoring of MN. Subsequent studies have further identified a variety of other target antigens, such as thrombospondin type-1 domain-containing 7A (THSD7A), neural epidermal growth factor-like protein 1 (NELL1), and exostosin 1 (EXT1)/exostosin 2 (EXT2), among others.³ Currently, the diagnosis of MN mainly relies on renal biopsy and serum autoantibody testing yet both traditional methods have significant limitations. Renal biopsy is an invasive procedure and cannot dynamically reflect disease progression. Serologic testing for some MN target antigens (e.g., THSD7A) is limited to specialized laboratories.¹ A recent study by Lahme et al. published in *Cell*, reveals a groundbreaking discovery that urinary autoimmunoglobulin-triggered extracellular vesicles (AIT-EVs) serve as a non-invasive diagnostic tool for sensitively detecting and monitoring renal autoimmune activity in patients with membranous nephropathy (MN) and even autoimmune kidney disease.⁴ This commentary will delve into the core findings, mechanistic insights of the study, as well as its transformative implications for the diagnosis and treatment of MN. To provide a concise visual overview of these key aspects, we have constructed a

schematic illustration that synthesizes the study's core framework (Figure 1).

CORE FINDING: URINARY AIT-EVS AS A PATHOPHYSIOLOGICAL MARKER OF MN

Lahme et al. observed that urinary AIT-EVs from membranous nephropathy (MN) patients exhibit distinct molecular profiles compared to those from healthy individuals and non-MN nephrotic patients. These vesicles originate from the plasma membrane of podocyte foot processes and are released into the urine, serving as indicators of renal autoimmune activity. Specifically, urinary AIT-EVs are characterized by the co-expression of disease-specific autoantibodies, such as anti-PLA2R1 and anti-THSD7A, and their target antigens, alongside podocyte-specific proteins like nephrin and podocin. What sets AIT-EVs apart from conventional extracellular vesicles is their enrichment in 14-3-3 proteins, which are known to regulate membrane budding and aggregate formation. This distinct composition enhances their reliability as biomarkers in MN.

Clinical validation studies have demonstrated that urinary AIT-EVs correlate highly with glomerular immune aggregates of MN. Longitudinal monitoring in a cohort of MN patients indicates that the abundance of urinary AIT-EVs, along with autoantibodies they carry, closely correlates with disease activity, even when serum autoantibody levels are undetectable. In a prospective study, five cases classified as seronegative by traditional methods were identified as PLA2R1-associated MN by urinary AIT-EVs, demonstrating their diagnostic value. Furthermore, in relapsing THSD7A-associated MN patients, bound autoantibodies were detected within AIT-EVs during clinical remission, when serum levels were undetectable, enabling the capture of subclinical activity with a significant advantage over traditional diagnostic methods that can lack sensitivity or be invasive.

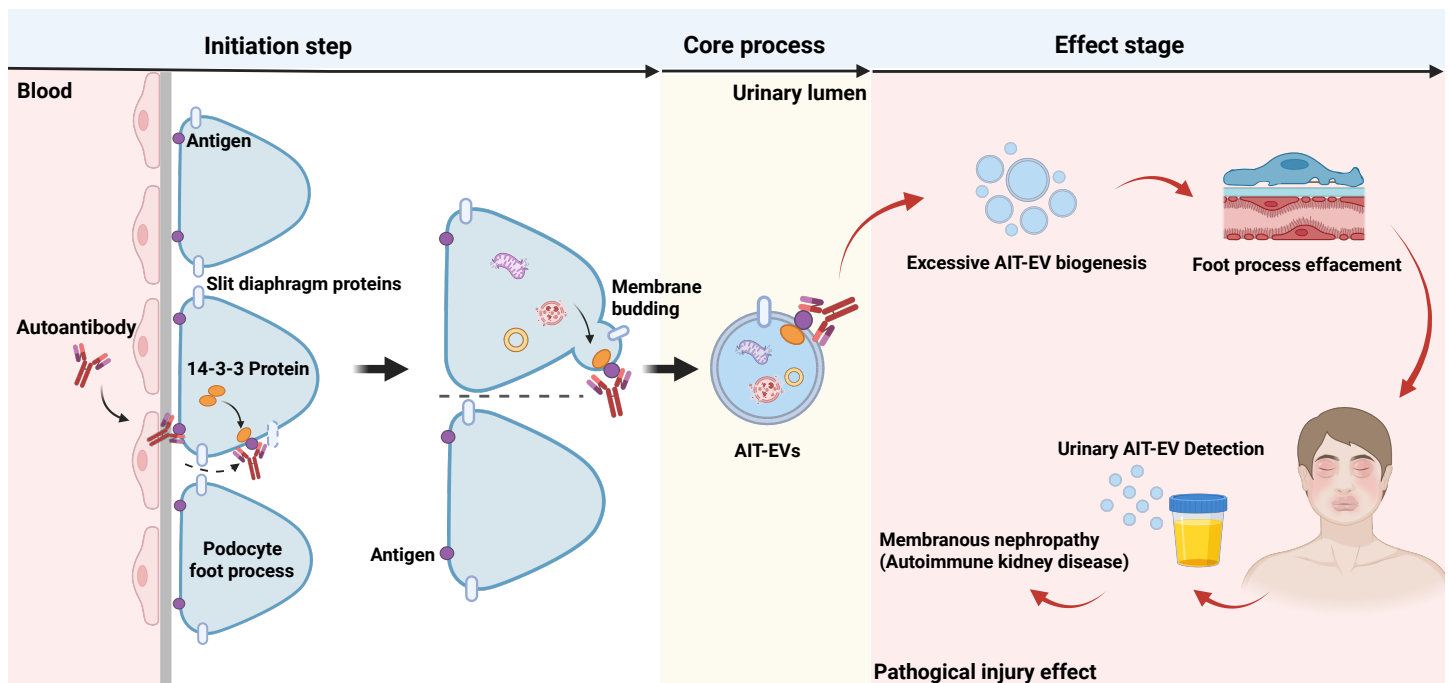


Figure 1. A new non-invasive approach using urinary AIT-EVs for the diagnosis of membranous nephropathy This schematic illustrates that autoantibodies bind podocyte antigens (e.g., PLA2R1, THSD7A), triggering membrane budding via 14-3-3 recruitment, ultimately forming AIT-EVs. Excessive AIT-EVs induce podocyte injury and MN.

Animal models support the critical role of AIT-EVs in MN pathogenesis. In a murine model of THSD7A-induced MN, pathogenic autoantibodies triggered significant AIT-EV release, correlating with elevated clinical disease activity scores. The secretion levels of urinary AIT-EVs matched the severity of podocyte foot process effacement, a key pathological feature of MN. Gene knockout of ADAM10, a metalloproteinase involved in shedding podocyte surface antigens, increased AIT-EV formation, exacerbated foot process effacement, and enhanced the clearance of glomerular immune complexes. Collectively, these findings provide strong evidence of a direct causal relationship between AIT-EV generation, glomerular immune homeostasis, and podocyte injury in MN.

MECHANISM ELUCIDATION: AIT-EVS LINK IMMUNE COMPLEX CLEARANCE AND PODOCYTE INJURY

Lahme et al. conducted a comprehensive study to investigate the role of AIT-EVs in MN pathology, specifically focusing on the 14-3-3 proteins and ADAM10 sheddase. Their findings revealed that AIT-EVs are crucial for managing the glomerular antigen-autoantibody burden, as these vesicles contain both antigens and autoantibodies. Importantly, AIT-EV formation appears to function as a compensatory mechanism that facilitates the removal of subepithelial immune complexes and intracellular waste, thereby reducing the glomerular immune burden. Immunofluorescence studies demonstrated the presence of significant aggregates in the glomerular urinary space, confirming a strong correlation between murine models and patients with THSD7A-positive MN. The study indicated that AIT-EV release is linked to the efficiency of glomerular immune complex clearance, as increased urinary AIT-EV abundance corresponded with lower glomerular antigen and insoluble autoantibody levels.

Furthermore, Lahme et al. explored the relationship between AIT-EV release and podocyte injury, characterized by foot process effacement. In THSD7A+MN mice, severe podocyte injury and elevated clinical disease scores were observed. Notably, a correlation was found between the extent of foot process effacement and urinary AIT-EV release, suggesting a direct mechanistic involvement. Thus, while AIT-EV formation contributes to immune complex clearance, excessive or sustained release appears to occur at the expense of filtration barrier integrity. The study further showed that ADAM10 deletion increased AIT-EV formation and aggravated disease severity, suggesting that impaired antigen shedding promotes AIT-EV formation while exacerbating podocyte injury.

The study also proposed a computational image algorithm to analyze glomerular antigen deposition patterns in MN patients, particularly those with PLA2R1-positive MN. This algorithm assessed the density of PLA2R1 aggregates in biopsies to differentiate between remission and non-remission groups. A low density score indicated effective clearance through AIT-EV formation, while a high score suggested a burdened state with dense deposits. These findings suggest that the presence and dynamics of podocyte-bound and urinary-released AIT-EVs are significant in managing glomerular antigen-autoantibody aggregates. The study portrays AIT-EVs as a double-edged response: a protective pathway for immune complex disposal that, when excessive, contributes to structural podocyte damage. Overall, the study highlights a critical pathway by which AIT-EVs serve as a mechanism for glomerular exit of pathogenic aggregates, ultimately impacting both podocyte health and clinical outcomes in MN.

CLINICAL SIGNIFICANCE AND FUTURE DIRECTIONS

This study introduces AIT-EVs as a non-invasive diagnostic and prognostic tool for managing MN, addressing traditional limitations by directly reflect-

ing podocyte activity. Testing for urinary AIT-EVs enables diagnosis and monitoring, particularly in seronegative patients, by detecting vesicle-bound antibodies.

Moreover, AIT-EV biogenesis may serve as a therapeutic target, allowing modulation to balance immune-complex clearance and podocyte protection. Enhancing AIT-EV production may mitigate tissue damage in cases of excessive immune complex deposition, while inhibiting their generation could preserve podocyte function in severe cases.

Although the pathobiological process of podocyte AIT-EV formation helps explain various aspects of glomerular protein accumulation, immune complex clearance, and foot process (FP) effacement in MN, several questions remain. The mechanisms by which membrane-bound aggregates reach the urinary side of podocyte membranes are unclear, necessitating further live imaging and in situ studies. Additionally, assessing causality between AIT-EV abundance and FP effacement requires interventions that either enhance or inhibit AIT-EV release. Future research should focus on elucidating the signaling pathways involved in AIT-EV biogenesis and validating their role across various podocyte injuries. Further studies are needed to validate the clinical utility of AIT-EVs in podocytopathies.

CONCLUSION

This study highlights a paradigm shift in MN research by identifying urinary AIT-EVs as key mediators between immune complex clearance and podocyte injury. Urinary AIT-EVs provide a non-invasive diagnostic tool for detecting disease-causing autoantibodies, complementing serum measurements and kidney biopsies, which enhances early disease detection, accurate subtyping, and personalized treatment strategies for MN. Although the current evidence is primarily derived from MN, this innovative, non-invasive approach may have implications for other immune-mediated podocytopathies, including minimal change disease and primary focal segmental glomerulosclerosis. However, its broader applicability warrants further investigation. In these conditions, autoantibodies targeting nephrin have been identified,⁵ suggesting a broader relevance of urinary AIT-EVs in the diagnosis and therapy of these autoimmune kidney diseases.

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FUNDING AND ACKNOWLEDGMENTS

Not applicable.

AUTHOR CONTRIBUTIONS

Conceptualization: Xiaozhao Li, Enyu Qi; Writing – Original Draft: Enyu Qi; Writing – Review & Editing: Xiaozhao Li. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.