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Letter to the Editor

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The Significance of Anti-PLA2R in Diabetic Kidney Disease: Truly a False Positive?

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Diabetic kidney disease (DKD) is one of the leading causes of end-stage kidney disease worldwide. Proteinuria in patients with diabetes is typically attributed to the natural history associated with DKD progression. Diagnosis of DKD is usually based on the duration of one's diabetes, their glycemic control over time, i.e., HbA1c levels, and the presence of other diabetic complications such as retinopathy. It is frequently observed that patients with newly diagnosed DKD present in combination with diabetic nephropathy or other glomerular and tubular diseases. Indeed, previous studies highlighted that in diabetic patients presenting with nephrotic-range proteinuria, the prevalence of concurrent kidney disease could be as high as 37.2% [1]. Kidney diseases could be often misdiagnosed, however, without confirmation from a biopsy. Kidney biopsy is an invasive procedure with potentially severe bleeding-related complications. Thus, there is an unmet critical need for noninvasive diagnostic methods to detect kidney disease in diabetic patients presenting with significant proteinuria.

Among the various etiologies of glomerular diseases that are associated with diabetic patients, primary or idiopathic membranous nephropathy (IMN) and IgA nephropathy were reported to be the most common pathologies [2, 3]. In a single-center observational study from China involving 982 patients with type 2 diabetes mellitus (T2DM) who underwent kidney biopsy and were included in the final analysis, Liu et al. [3] noted 64% of patients with nondiabetic kidney pathologies of which membranous nephropathy and IgA nephropathy each constituted 31% of the histopathological diagnoses detected. The M-type phospholipase A2 receptor (PLA2R), a transmembrane receptor on glomerular podocytes, was identified as the major antigenic target in IMN in 2009 [4]. Circulating autoantibodies of PLA2R (i.e., anti-PLA2R) have been utilized as a diagnostic marker in IMN and to monitor disease activity and therapeutic response [5]. These antibodies can be detected using the Western blot technique, indirect immunofluorescence testing (IIFT), and now also by enzyme-linked immunosorbent assay (ELISA). While analysis by Western blot, as per the seminal original study conducted by Beck et al. [4],

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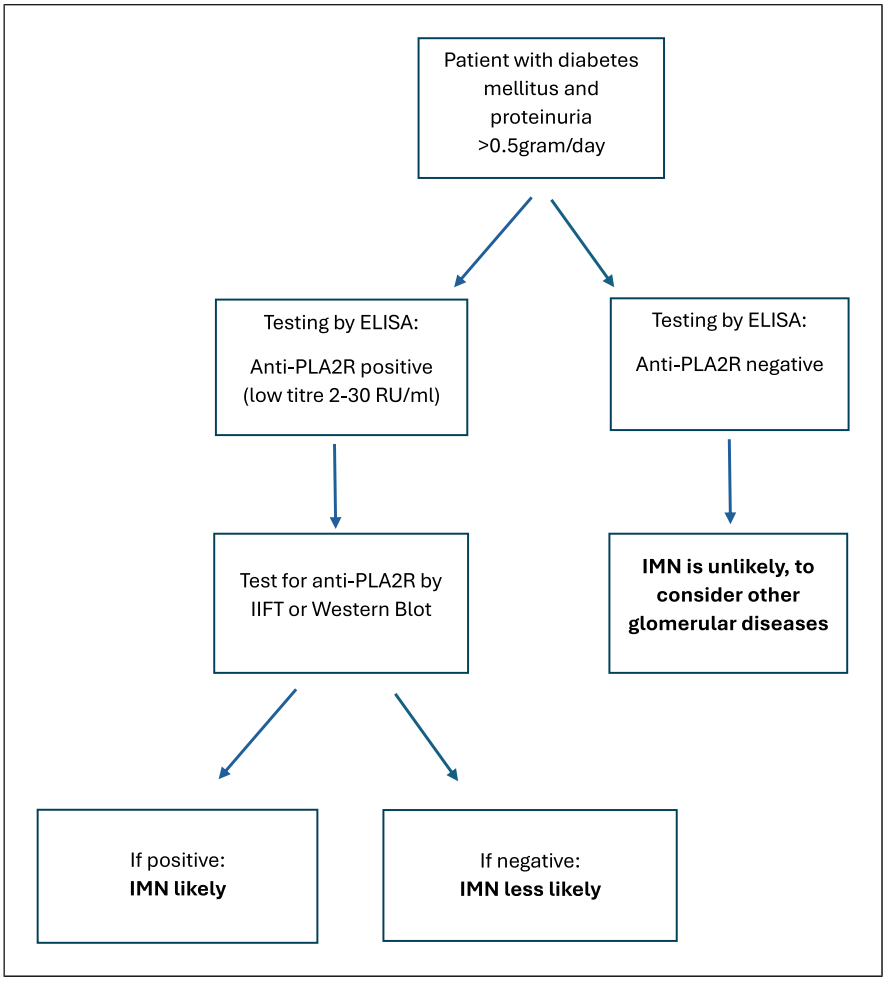

Fig. 1. A proposed approach for anti-PLA2R antibody testing to diagnose glomerular disease in diabetic patients. ELISA, enzyme-linked immunosorbent assay; IIFT, indirect immunofluorescence test; IMN, idiopathic membranous nephropathy.

remains the most sensitive option, this is not commercially available at present and would be challenging to incorporate for routine processing within the clinical setting. IIFT and ELISA have often been used for clinical assays. Importantly, ELISA testing provides quantitative results, which aids in monitoring disease activity. The anti-PLA2R antibody has been shown to be a sensitive and specific biomarker of IMN across all assays. A meta-analysis of 9 studies including 2,212 patients concluded the sensitivity of anti-PLA2R for the diagnosis of IMN to be 78% and its specificity to be 99% [6]. Anti-PLA2R positivity has been documented in between 70 and 83% of IMN cases, but can also occasionally be present in secondary membranous nephropathy and non-membranous nephropathy cases [7, 8]. As determined in the 2021 Kidney Disease Improving Global Outcomes (KDIGO) guidelines, a kidney biopsy is not needed to diagnose IMN in patients presenting with nephrotic syndrome and anti-PLA2R positivity [9].

The question which subsequently arises is whether anti-PLA2R can be used as a noninvasive diagnostic marker to identify IMN in diabetic patients without the requirement for a confirmatory kidney biopsy. Zhang et al. [10] studied 87 patients with T2DM and proteinuria >0.5 g/day who had a kidney biopsy, 29% (i.e., 25 patients) were reported to have diabetic nephropathy, 53% reported to have IMN, and 18% reported to have other pathologies. Among the 25 patients reported with diabetic nephropathy, only 1 patient had positive anti-PLA2R antibody test results. Another study by Wang et al. [11] evaluated 227 patients with T2DM. A total of 46% of patients had a biopsy diagnosis of diabetic nephropathy, while 20% had IMN. None of the patients diagnosed with diabetic nephropathy had positive anti-PLA2R antibodies, while this was reported for 60% of patients with IMN.

On the other hand, there were reports where anti-PLA2R antibodies were found to be "falsely positive" in patients presenting with nephrotic syndrome secondary

to diabetes. Hoxha et al. [12] reported a case of a 74-year-old patient with long-standing type 2 diabetes with nephrotic-range proteinuria, who was noted to have anti-PLA2R positivity. Testing on four samples over a 6-month period, levels ranging between 120 and 258 RU/mL were detected on ELISA (the cutoff for positivity is >20 RU/mL). However, in contrast to the ELISA results, the antibodies were negative when tested using IIFT. The case patient had two kidney biopsies 1 month apart which displayed no histopathological signs of IMN but instead had features suggestive of diabetic glomerulosclerosis. This was due to the cross-reaction of the His-antibody, demonstrated when His-Tag peptide was applied to the biopsy sample. Caza et al. [13] subsequently also described 2 cases that presented with anti-PLA2R positivity by ELISA but were negative by IIFT. Both patients were eventually diagnosed with DKD upon a kidney biopsy. The reports by Hoxha et al. [12] and Caza et al. [13] each demonstrate the low specificity of ELISA. IIFT is found to be more sensitive in comparison with ELISA for the detection of anti-PLA2R when the cutoff for positivity on ELISA is determined at >20 RU/mL. There may be a benefit in conducting confirmatory IIFT for the primary diagnosis of IMN in addition to ELISA testing. IIFT may be followed by sequential ELISA testing to evaluate disease progression and response to therapy.

In summary, the discovery of the PLA2R antigen in 2009 has certainly transformed our comprehension and approach to the paradigm of diagnosing and managing IMN. The current literature nevertheless remains unestablished as to whether diabetic patients suspected of IMN based on anti-PLA2R positivity should forgo a confirmatory kidney biopsy. Clinicians should be cautious when interpreting anti-PLA2R results from diabetic individuals and be aware of the possibilities regarding "false positives." The use of multiple appropriate serological testing modalities in determining anti-PLA2R status, including IIFT and perhaps also Western blot, is recommended for clarity whenever required. Based on current evidence, Figure 1 illustrates our proposed approach to anti-PLA2R antibody testing for a diabetic patient presenting with nephrotic-range proteinuria. Ultimately, a formal tissue diagnosis remains the gold-standard diagnostic option in diabetic patients for now, especially in those presenting with proteinuria and lower eGFR levels. Further study will be needed to evaluate the utility of anti-PLA2R to diagnose glomerular disease(s) in diabetic patients.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

Conceptualization: H.H.L.W. and R.C. Resources: A.D., H.H.L.W., and R.C. Writing – original draft preparation: A.D. Writing – review and editing: H.H.L.W., D.A.K.K., and R.C. Visualization: H.H.L.W., D.A.K.K., and R.C. Supervision: D.A.K.K. and R.C. Project administration: H.H.L.W. All authors have read and agreed to the published version of the manuscript.

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