

# Anti-phospholipase A2 receptor antibody in idiopathic membranous nephropathy: New concepts

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Membranous glomerulopathy is a major glomerulonephritis that often causes nephrotic range proteinuria in adults.<sup>[1-4]</sup> Idiopathic membranous nephropathy (iMN) has been found of having an immune etiologic basis. Various data such as kidney biopsy findings on light microscopy, immunofluorescence staining for granular immunoglobulin G (mainly IgG4) and C3 deposition along the glomerular basement membrane, electron-dense deposits of immune complexes in the sub-epithelial glomerular basement membrane and the association with complement activation products and disease activity all reiterated that immune dysfunction underlies the disease.<sup>[5-14]</sup> Glomerulopathy of membranous can also be secondary to some infections, an autoimmune diseases, drugs and various malignancies.<sup>[1,3,15]</sup> In iMN, disease can be developed due to the binding of a circulating antibody to an antigen that is presented on podocytes.<sup>[1,3,15-21]</sup> Currently, various therapeutic modalities are available; however, some patients with iMN may experience spontaneous remission.<sup>[1,3,8,21-24]</sup> In contrast, in a substantial number of patients the answer to treatment is poor and the risk of renal failure remains high. It was observed that iMN may lead to chronic renal failure among 40-50% of adults patients in long-term.<sup>[1,3,8,9,17]</sup> Some factors such as, age, renal function, amount of proteinuria and gender of patients can be encountered to describe patients at risk.<sup>[15,16,24-29]</sup>

However, these factors may not so relevant predictors for exact prediction the course of the disease or for intensification or cession of immunosuppressive therapy in this disease.<sup>[1,15,16,24]</sup> In fact, in some individuals with large proteinuria, spontaneous remission may occur in up to 20-25% of cases.<sup>[1,15,16,24]</sup> Thus, a predictor for disease activity and/or treatment effects would be a very suitable tool for therapy decisions of membranous nephropathy. Hence, prognostic biomarkers in iMN would aid clinicians to identify potential candidates to early intervention and specific strategies.<sup>[1,15,16,24]</sup> Recently, M-type phospholipase A2 receptor (PLA2r) was recognized as the target antigen of autoantibodies in adults with iMN.<sup>[24-32]</sup> The PLA2r is a type I

transmembrane glycoprotein related to the C-type animal lectin family like the mannose receptor. More recent observations, revealed that antibodies to the PLA2r are IgG4.<sup>[24,31,32]</sup> These IgG4 antibodies can be identified in the glomerular immune complexes and they co-localize with PLA2r. Moreover, in secondary forms of membranous nephropathy, such IgG4 antibodies are lacking or less prevalent.<sup>[24,32,33]</sup> Interestingly, a bulk of studies have shown that autoantibodies against PLA2r not only have a direct pathogenic function, but also act as sensitive and specific markers for iMN.<sup>[24,31-36]</sup> Indeed, the detection of autoantibodies against PLA2r in patients with iMN gives a new chance to improve the knowledge and clinical management of membranous nephropathy.<sup>[34-37]</sup> Thus, evaluating anti-PLA2r serum levels in patients with Nephrotic syndrome should define a probable diagnosis of iMN.<sup>[24,31-37]</sup> Even in individuals in whom iMN has a pathology confirmation needs anti-PLA2r serum levels may be a determining factor to rule out secondary forms of membranous glomerulopathy.<sup>[24,32-37]</sup> Furthermore, level of anti-PLA2r may be used as a marker of answer to treatment too.<sup>[24,32-37]</sup> However, published data revealed some inconsistencies in results regarding the relationship between anti-PLA2r level and the clinical presentation.<sup>[31,32,34]</sup> There may be several reasons for these discordance; such as, different stages of membranous nephropathy could lead to an inappropriate interpretation. Furthermore, the methods of measurement and titrating of anti-PLA2r were different among the published studies and importantly, most of the previous investigations did not include a reasonable number of patients.<sup>[24,31-34]</sup> Currently, antibodies to PLA2r are found in 60-80% of patients before immunosuppressive treatment and are only occasionally found in secondary membranous nephropathy. Importantly, they have not been observed in other pathological conditions and in healthy individuals.<sup>[24,31-34]</sup> However, several investigators have addressed the occurrence of anti-PLA2r antibodies in patients with secondary membranous nephropathy; thus, more data are still required before we can securely conclude that there is no need to investigate for an underlying cause.<sup>[38-41]</sup> Since PLA2r antibodies have

not been identified in healthy persons and on the other hand, proteinuria due to other glomerular diseases such as, focal segmental glomerulosclerosis, IgA nephropathy or minimal change glomerulopathy, was associated with negative PLA2r antibodies; however, it should be pointed out that the numbers of publications on this subject in the literature are small and it still needs further researches.<sup>[39-42]</sup>

Measurement of anti-PLA2r is now commercially available to use and assess. We therefore, suggest keeping serum samples at baseline and during follow-up of patients with membranous nephropathy.<sup>[40-44]</sup> This would permit to achieve measurements at a time point when all questions regarding the efficiency of anti-PLA2r antibody measuring in patients with iMN fully resolved. We suppose that it is too soon to discard a kidney biopsy in patients with Nephrotic syndrome. In fact like every real science, further studies deepening our understanding could make more complexity for us or even shed doubts on the role of serum anti-PLA2r as the main pathogenic antibody in iMN, but at this moment, we should rely on our recent achievements.

Thus, at this stage we can conclude that anti-PLA2r antibody may cause damage to the kidney directly, high levels of anti-PLA2r antibodies are linked with active disease and a higher risk of declining renal function and a patients with a high antibody burden may benefit from earlier therapeutic intervention.<sup>[43-46]</sup> However, further studies are still necessary for better understanding of the role anti-PLA2r antibody in iMN.

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