

Review Article

Is There A Diagnostic And Prognostic Role For Anti-Nephrin Autoantibodies In Diabetic Nephropathy?.

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Abstract

One of the main causes of end-stage kidney disease worldwide, particularly in affluent nations, is diabetic nephropathy (DN). Microalbuminuria is a hallmark of the traditional pathogenic progression of DN, which leads to nephrotic-range proteinuria and renal function loss. In individuals with DN, the level of albuminuria is thought to be a separate risk factor for all-cause death. It is now commonly known that abnormalities in podocyte structure and function are the cause of albuminuria. A significant part of the glomerular filtration barrier is played by podocytes.

Since the nephrin protein is a fundamental part of the podocyte's slit diaphragm, it has been well documented that DN and other proteinuric glomerulopathies have downregulated nephrin expression. Prior research has demonstrated that urine nephrin may be an early indicator of podocyte damage in DN. The pathophysiology of podocytopathies may be influenced by circulating autoantibodies that target nephrin, according to a growing body of research in recent years.

Nevertheless, nothing is known about the functional importance of these circulating autoantibodies in DN patients. Based on the literature currently available, we hope to assess the importance of nephrin dysregulation in the pathophysiology of DN in this review. We also hope to give a summary of the use of circulating anti-nephrin autoantibodies in relation to their diagnostic and prognostic role in podocytopathies, including DN.

Keywords : *anti-nephrin; nephrin; diagnostic biomarker; prognostic biomarker; diabetes mellitus; diabetic nephropathy.*

INTRODUCTION

The Current State of Diagnostic Approaches in Diabetic Nephropathy

According to reports, the prevalence of diabetes has risen to epidemic proportions globally, and up to 40% of diabetics develop diabetic nephropathy (DN) [1]. Therefore, in both industrialized and developing nations, DN is anticipated to remain the primary cause of end-stage renal disease. Current guidelines are currently centered on creating solutions that enable early identification and complete care of DN in order to decrease its occurrence and progression. This include controlling cardiovascular risk factors, such as maximizing blood pressure control, and altering lifestyle choices to attain stringent glycemic control.

The clinical characteristics of DN are now understood to be the progression of albuminuria from microalbuminuria to

nephrotic-range proteinuria at the same time as a progressive deterioration in kidney function. Currently, the only recognized biomarker for early DN detection is albuminuria. Additionally, published research shows that the degree of albuminuria positively correlates with the development of cardiovascular events and the progression toward end-stage kidney disease, making it a crucial prognostic factor for all-cause mortality. Kidney Disease Improving Global Outcomes (KDIGO) guidelines are typically followed when categorizing albuminuria.

Increased salt and glucose reabsorption facilitated by sodium-glucose cotransporters during the hyperglycemic state drives glomerular hyperfiltration, which is the most commonly recognized pathophysiological mechanism of albuminuria in DN [4]. When salt and glucose reabsorption rises in DN, dysregulated tubuloglomerular feedback is triggered through the macula densa cells. The efferent glomerular arteriole's

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vascular resistance rises as a result, while the subsequent afferent arteriole's vascular resistance paradoxically falls, raising the glomerular pressure in the hyperfiltration state. The glomerular filtration barrier will then be lost as a result of a series of processes including podocyte oxidative stress, separation, inflammation, and scarring.

The accurate identification of DN's clinical symptoms has been the primary basis for diagnosing DN in practice. This would entail considering the person's history of glycemic management, albuminuria trajectory, and the existence of additional diabetes-related macro- or microvascular problems, such as diabetic retinopathy. The blood creatinine levels of the individual, which are frequently utilized as a marker reflective of the estimated glomerular filtration rate (eGFR), will then be associated with it. Nonetheless, data from multiple observational studies revealed a significant percentage of concurrent non-diabetic nephropathies discovered during kidney biopsies in diabetic patients, which may call for alternative therapeutic modalities. Liu et al. conducted the largest study to date, retrospectively analyzing kidney samples from 982 individuals with type 2 diabetes who were above the age of 18 across a ten-year period. It was shown that 64% of the individuals had kidney problems other than diabetes.

Liu et al. retrospectively examined the kidney biopsies of 982 type 2 diabetes patients over the course of ten years, in the largest study to date. It was discovered that non-diabetic renal problems were present in 64% of the individuals [5]. Given the invasive nature of the treatment and the possibility of bleeding, which could result in nephrectomy and mortality, the growing use of kidney biopsies in diabetic patients with renal disease is still up for debate. As a result, there is an increasing demand for noninvasive diagnostic alternatives that would eliminate the necessity for kidney biopsies in the majority of patients, such as certain urine and serum indicators and sophisticated imaging techniques.

In contrast to albuminuria, a number of other diagnostic biomarkers of DN have been investigated and have shown promise as potentially helpful noninvasive techniques in identifying kidney impairment in DN early on. Cystatin C, a protein of the cysteine protease inhibitor family that is readily filtered by the renal glomeruli because of its low molecular weight, is an example of a promising biomarker in the early detection of DN. Jeon et al. first investigated this in human subjects, enlisting 332 type 2 diabetes patients with normoalbuminuria and various levels of albuminuria. Jeon et al. showed a significant correlation between an increase in the degree of albuminuria and rising levels of cystatin C in the urine and serum.

Additionally, using the conventional creatinine-based Modification of Diet in Renal Disease equation in patients with normoalbuminuria, both serum and urinary cystatin C were

found to be independent factors associated with an eGFR < 60 mL/min/1.73 m² when a multivariate logistic regression analysis was applied. This supports the idea that, even in patients who are not albuminuric, the presence of cystatin C in blood and urine may serve as the foundation for early detection and progression prediction of DN. Nevertheless, this investigation was constrained by its retrospective cross-sectional study methodology and rather small sample size. Therefore, it is still unclear whether there is a real correlation between the progression of the disease and the different risk factors associated with DN patients. Cystatin C will be the subject of larger prospective research as a potential biomarker in clinical practice.

Nephrin and the Kidney Filtration Barrier in Diabetic Nephropathy

Our knowledge of the glomerular filtration barrier at the molecular level has been completely transformed since the identification of the NPHS1 gene mutation in congenital nephrotic syndrome of the Finnish type more than 25 years ago. This gene mutation encodes the transmembrane protein nephrin [12]. The structural part of the glomerular podocytes' slit diaphragm, which primarily controls the glomerular filtration barrier's size selectivity, is made up of several protein components, including nephrin [13]. Additionally, nephrin tyrosine phosphorylation creates a complex signaling platform that interacts with other phosphorylated protein tyrosine sites [14,15]. This will therefore affect a podocyte's shape and cell adhesion, controlling the glomerular podocytes' structural and functional integrity.

Aaltonen et al. and Forbes et al. first used streptozotocin-induced mouse kidney models to investigate the role of nephrin in DN pathophysiology because DN is known to be a major cause of podocyte dysfunction and the ensuing albuminuria. This causes diabetes by specifically impairing insulin production in pancreatic beta cells [17,18]. Nephrin gene expression in the kidney was detected by immunohistochemistry in both investigations, and it was measured by real-time polymerase chain reaction (PCR). Within 6–8 weeks of the onset of diabetes, both studies demonstrated an initial two–threefold increase in nephrin messenger ribonucleic acid (mRNA) expression in the glomerulus of the diabetic animal models. Concurrently, Aaltonen et al. used a model of spontaneous non-obese diabetic mice to duplicate these findings.

Doublier et al. were able to apply these results to kidney biopsies of 23 patients with type 1 and type 2 diabetes in addition to the aforementioned experimental reports [19]. Immunofluorescence showed a significant decrease in nephrin expression in the human glomeruli of diabetes patients with microalbuminuria as compared to their healthy controls. These results were further supported by Jim et al.

in a study that used immunohistochemistry to show that 15 kidney biopsies from individuals with type 2 diabetes had downregulated nephrin and other podocyte-specific proteins when compared to a control group [20]. Nephrin dysregulation was therefore thought to be a significant factor in the onset of albuminuria in DN.

Urinary Nephrin: A Novel Biomarker for Early Diabetic Nephropathy

Despite being the gold standard for the early diagnosis and prognosis of DN, microalbuminuria's sensitivity and specificity are still debatable given the available data. Other pathological conditions such urinary tract infections, heart conditions, and any acute sickness that causes hemodynamic stress are also associated with microalbuminuria. Thus, the development of diagnostic and prognostic indicators for early DN symptoms other than albuminuria is necessary. It is commonly acknowledged that podocyte damage in DN causes different protein fragments to be excreted into urine. Therefore, research has focused on a variety of urine indicators to support the early detection, prevention, and treatment of DN.

Jim et al. also looked at the relationship between DN and urine nephrin in a small group of people with type 2 diabetes who had different levels of albuminuria [20]. ELISAs, or enzyme-linked immunosorbent tests, were used to assess urinary nephrin. Nephrinuria was shown to be present in 54% of diabetic patients without microalbuminuria and in all patients with microalbuminuria. A decrease in eGFR was favorably connected with urinary nephrin levels, which also had a strong positive association with albuminuria. According to these findings, nephrinuria can appear in early DN prior to microalbuminuria and an increase in urine nephrin levels in overt illness.

More recently, a cross-sectional study by Kostovska et al. and a case-control study by Veluri et al. that included type 2 diabetes patients with or without a diagnosis of DN and matched healthy controls further supported the importance of urinary nephrin as an early biomarker of DN [22, 23]. Urinary nephrin has a high diagnostic sensitivity of up to 100% and specificity of up to 88% as a biomarker of early DN, according to both investigations. In people with DN, nephrinuria likewise has a 96% predictive probability. Additionally, this study confirmed that urine nephrin levels and eGFR have a substantial negative connection, suggesting that this is an early indicator of poor kidney function.

Urinary nephrin may be a better early indicator for pre-clinical DN than microalbuminuria, according to all human investigations conducted to date. However, the small sample sizes of these research limited their applicability. The researchers also admitted that the study design of all of the published studies was insufficient to reliably forecast the

future course of DN in individuals with pre-clinical DN or to show a causal mechanism of nephrinuria. These knowledge gaps might be filled in the future by a sizable prospective study comprising individuals with non-albuminuric diabetes. A follow-up time of at least ten years after the beginning of diabetes would be appropriate for these validation investigations.

Anti-Nephrin Autoantibodies and Their Role in Diabetic Nephropathy

Watts et al. initially identified circulating anti-nephrin autoantibodies in a subgroup of children and adults with biopsy-proven minimal change disease (MCD), a well-known cause of nephrotic syndrome, in their seminal work that was published in the Journal of the American Society of Nephrology in 2021. The absence of a discernible pathological alteration in the renal glomeruli under light microscopy is a characteristic of MCD. However, podocyte foot effacement and fusion, two signs of significant podocyte injury, will be shown by electron microscopy ultrastructural investigations. The capacity of plasma taken from nephrotic syndrome people to cause proteinuria in non-nephrotic subjects was shown by earlier observational studies reported as early as 1954. As a result, there has been a lot of attention over the years to determine whether certain circulating components made from lymphocytes are involved in the pathophysiology of MCD.

There is currently a startling lack of information regarding the uses of anti-nephrin autoantibodies in DN, despite earlier strong evidence of nephrin dysregulation in DN and the active role of circulating anti-nephrin autoantibodies in causing podocyte disruption. The prevalence and function of autoantibodies with nephrin in patients with type 1 diabetes have only been examined in one study to date, which was published by Aaltonen et al. in 2007 [36]. This study used a ra-dioimmunoprecipitation test to assess anti-nephrin autoantibodies in stored serum samples from 66 children and adolescents with type 1 diabetes and 96 non-diabetic control patients during a 10-year period following the initial diabetes diagnosis.

A recent large, multicenter investigation by Hengel et al. confirmed that a considerable percentage of adults and children with podocytopathies such MCD, primary focal segmental glomerulosclerosis (FSGS), and idiopathic nephrotic syndrome (INS) had anti-nephrin autoantibodies [31]. Using a sensitive hybrid immunoprecipitation ELISA, the prevalence of these autoantibodies was found to be as high as 69% in adults with untreated active MCD and 90% in children with untreated active INS. Furthermore, in anti-nephrin autoantibody-associated podocytopathies, there was a strong correlation between proteinuria and anti-nephrin autoantibody levels and disease activity. Longitudinal

measures of anti-nephrin autoantibodies in a subset of 18 children with INS, 13 people with MCD, and 5 adults with primary FSGS were used to support this.

Then, utilizing an experimental mouse model actively inoculated with recombinant murine nephrin, this work confirmed a causal link between anti-nephrin autoantibodies and podocyte dysfunction. After being immunized, these mice mimicked the clinicopathological characteristics of MCD by developing circulating anti-nephrin autoantibodies and nephrotic syndrome. Gold labeling of mouse immunoglobulin (IgG) was isolated at the slit diaphragms, particularly in regions with diffusely effaced podocyte foot processes, as demonstrated by electron microscopy. Additionally, nephrin tyrosine phosphorylation was elevated in the glomeruli of immunized animals, according to proteomic and phosphoproteomic investigations. This changed the downstream signaling pathways, resulting in actin assembly, cytoskeletal remodeling, and nephrin endocytosis.

All things considered, the groundbreaking study by Hengel et al. presented a strong argument that circulating anti-nephrin autoantibodies actively contribute to the pathophysiology of podocytopathies rather than only serving as indicators of disease activity. This realization reinforced our focus on using certain kidney-specific autoantibodies rather than the histology description to diagnose glomerular disorders. It also raises the possibility of developing new, focused treatments [32]. Previous ground-breaking discoveries, such as autoantibodies against the non-collagenous domain of the type IV collagen on the glomerular basement membrane (GBM) in anti-GBM disease and autoantibodies against the phospholipase A2 receptor (PLA2R) in primary membranous nephropathy, support this [33, 34].

In a small subset of Japanese post-transplant patients with recurrent FSGS, Shirai et al. later provided evidence of the predictive significance of preexisting circulating anti-nephrin autoantibodies [35]. All 11 patients' kidney transplant biopsies after the recurrence of FSGS revealed increased nephrin phosphorylation and IgG deposition co-localized with nephrin, which is comparable to the animal model in the study by Hengel et al. Furthermore, it was verified that there was a substantial positive association between their individual serum anti-nephrin antibody levels. There is currently a startling lack of information regarding the uses of anti-nephrin autoantibodies in DN, despite earlier strong evidence of nephrin dysregulation in DN and the active role of circulating anti-nephrin autoantibodies in causing podocyte disruption.

Although it was observed that patients with a positive anti-nephrin autoantibody titre at any stage had a shorter mean duration of microalbuminuria manifestation than those with a negative test, this difference was not statistically significant. Consequently, the researchers were unable to

identify any meaningful causal relationship between the pathophysiological development of DN and circulating anti-nephrin autoantibodies. The screening approach used in this study was thought to be the reason for this negative discovery at the time; autoantibodies against the epitopes of just the intracellular portion of nephrin were assessed, suggesting that they might not have contributed to the pathophysiology of DN.

CONCLUSIONS

The discovery that nephrin is a crucial component of the glomerular filtration barrier has revolutionized our comprehension of the pathophysiology of podocytopathies. This additional information would be useful in shaping how nephrin-associated markers are used in clinical practice going forward. Even though DN is still the predominant cause of podocytopathy, nothing is known about the function of nephrin and anti-nephrin autoantibodies as an early diagnostic and prognostic indicator to gauge the course of kidney disease. It is yet unknown if this marker can be used to accurately distinguish DN from other proteinuric glomerulopathies such as minimum change disease, FSGS, and INS. However, the preliminary small-scale investigations that were published demonstrated that nephrin D.

However, nephrin dysfunction in DN was demonstrated by the published preliminary small-scale research, which led to nephrin breakdown and release through urine. Together with the groundbreaking finding regarding the application of circulating anti-nephrin autoantibodies in proteinuric glomerulopathies, these results can serve as the basis for further investigation into a different mechanism of podocytopathy in DN, which may transform our understanding of how to treat it.

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