REVIEW ARTICLE

Nephrin: An emerging biomarker for detecting damage of glomerular filtration barrier

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ABSTRACT

Nephropathy due to damage of filtration barrier is a primary origin of end stage renal disease in Diabetics. It is associated with considerable morbidity and mortality. Mostly clinicians rely on urine analysis of Albumin. In the recent years extensive research has been conducted to find out a novel biomarker which can help in the early diagnosis of nephropathy. A search was conducted regarding publications of new diagnostic biomarkers for nephropathy. Among many renal biomarker researched lately, Nephrin was identified as the one that can become an early predictor of nephropathy and the levels of which can also ascertain the severity of the disease.

KEY WORDS: *Nephrin, Microalbuminuria, Diabetic Nephropathy.*

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INTRODUCTION

According to International Diabetes Federation 366 million people are effected by diabetics and the figure estimated to rise to 552 million by year 2030.[1] In 2008 approximately 1.3 million deaths were related with diabetes[2], and in 2010 Van Dieren S. reported that Global excess mortality attributable to diabetes in adults was 3.8 million[3] out of which approximately 10% die of renal failure. Diabetes mellitus is well known for being the most important cause of end stage renal disease.[4] Almost 20 to 30% of all diabetics, Type I and Type II develop diabetic nephropathy.[5] Regarding the type of diabetes whether it is Type I or Type II diabetes, the risk of nephropathy is the same. But since the prevalence of Type 2 diabetes is greater than Type I, end stage renal failure secondary to Type II diabetes predominates.[6,7]

Nephropathy due to damage of filtration barriers in diabetes mellitus is considered as the most frequent microvascular complication[8] which clinically manifestS as increased excretion of protein in urine. Currently, the biomarker of diabetic Nephropathy is microalbuminuria (albumin >30 mg/g) in the urine. However, its involvement with development to renal failure is not well established, because microalbuminuria does not always direct to progressive kidney failure in diabetes mellitus.[9] Furthermore, microalbuminuria is also present in other diseases such as urinary tract infection.[10]

In the recent years extensive research has been conducted to discover a novel biomarker which would help in the early diagnosis of nephropathy. A search through internet was conducted looking for publications of new diagnostic biomarkers for nephropathy. Among many, Nephrin was identified as the superior biomarker that can become an early predictor of nephropathy. Secondly, the levels of nephrin were also found related with the severity of the disease.

DISCUSSION

Glomerular Filtration Barrier & Diabetic Nephropathy

The glomerular filtration barrier (GFB) prevents protein loss. Its three layers; endothelial cells, glomerular basement membrane and the podocytes complete the structure of GFB. The podocyte (visceral epithelial), are the cells surrounding the glomerulus. Filtration slits are the gaps between foot processes of podocytes.[11] These filtration slit are covered with slit diaphragm made up of nephrin.[12]

The precise pathogenetic mechanism of diabetic nephropathy has yet not been completely resolved. The Podocytes being the key structural elements in glomerular filtration barrier play an essential role in the progression of DKD and it is generally accepted that it occurs due to the injury of podocytes.[13] Hence, Podocytes and its specific proteins in urine may have potential role for the early diagnosis of DKD.[14]

Urinary Biomarkers & Nephropathy

Albumin is considered as a good indicator for glomerular damage.[15] But all diabetics with albuminuria do not develop progressive renal dysfunction.[16,17] Adler et al, in 2003 reported that 30% diabetics with renal destruction had normoalbuminuria.[18]

Transferrin is a protein with a mass that is slightly larger in size compared to albumin, but less anionic then albumin. Therefore it can be filtered more readily through the glomerular filtration barrier. It is an iron binding protein , and it helps in the transportation of ferric ions to all proliferative cells in the body.[19] The level transferrin has also been correlated with interstitial inflammatory cell and interstitial fibrosis.[20] Transferrinuria predicts that the patient has already developed microalbuminuria in type II diabetes mellitus[21], urinary transferrin excretion has a linear relationship or it is directly proportional to Urinary albumin excretion.[22] Urinary transferrin excretion is not only specific to diabetic nephropathy because its excretion also has been raised in diseases that affect the glomerulus sepcialy in primay glomerulonephritis.[23,24,25] Zho et al reported that contradictory results regarding the association of urinary transferrin excretion with duration of diabetes.[26]

Laminin, is a trimeric glycoprotein proteins that contain an α-chain, a β-chain, and a γ-chain, is a normal constituent of basement membranes. laminin is derived from the kidneys and in normal condition serum laminin cannot be filtered.[27] In case of diabetic nephropathy, Immunohistochemistry of nephron reveals the presence of laminin which is to be found in the mesangial expansion and thickened capillary basement membranes.[28] Urinary Laminin are associated with type IV collagen via fibronectin and entactin.[29]

Lipocalin-type prostaglandin D2 synthase is an enzyme synthesized by prostaglandin D2 . it is a secretary protein of the lipocalin superfamily . It has also been reported as a potential biomarker for diabetes.[30,31] In normal condition, Lipocalin-type prostaglandin D2 synthase (LPGDS) is present in the peritubular interstitium, while in diabetes mellitus it is present in the renal tubules. Although, the size of Lipocalin-type prostaglandin D2 synthase (L-PGDS) is small, the anionic charge is similar to albumin and it can pass easily through the glomerular capillary walls.[32]

Nephrin

Nephrin is the new biomarker which has been found to have diagnostic potential for detecting glomerular filtration barrier damage. Nephrin is a transmembrane protein necessary for the proper functioning of the renal filtration barrier and is a structural part of the slit diaphragm.[33] The actin cytoskeleton is attached to the scaffolding of the podocyte slit diaphragm via podocin and CD2AP, it associated protein is nephrin two domain extracellular and intracellular. The PI3K/AKT signaling pathway have functional characteristics with these proteins to maintain functional integrity.[34]

Structure of Nephrin

Nephrin is composed of eight extracellular immunoglobulin domains, one fibronectin domain, a transmembrane domain, and intracellular domain with nine tyrosine residues; Together it has 1241 amino acid residues, and molecular size of approximately 185 kda. The Immunoglobin like modules are type C2 which are found in many proteins involved in cell-cell or cell extracellular matrix interactions.[35] It has been speculated that tyrosine residues nephrin may have a role in podocyte cell adhesion and signal transduction. No marked similarity is observed in the cytosolic domain of nephrin with any known proteins.

Nephrin Gene Expression & Proteinuria

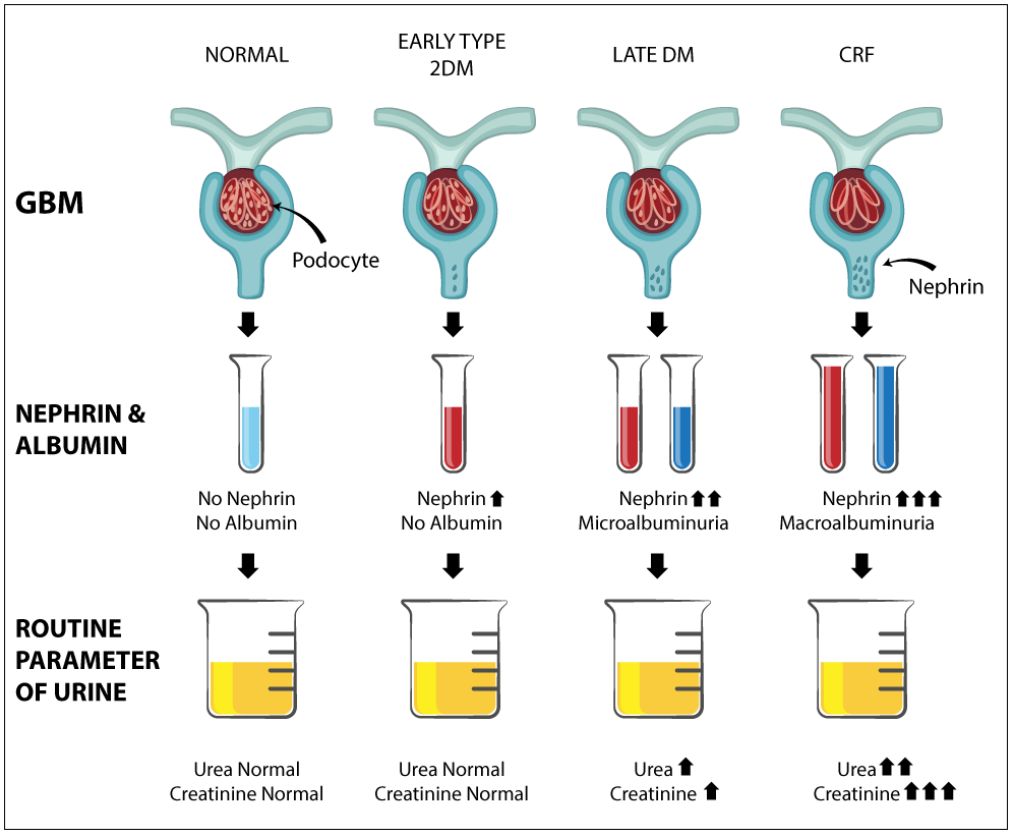
The expression and distribution of the four main podocyte molecules, podocin, alpha-actinin-4, CD2AP, and nephrin have change by the action of antiproteinuric effects of lisinopril, prednisone, and ATRA.[36] This antiproteinuric effect also exerted by PPRE (peroxisome proliferator-responsive elements). Enhancement of nephrin gene transcription[37] and some factors including bone morphogenetic protein 2, vascular endothelial growth factor (VEGF), fibroblast growth factor 1, insulin-like growth factor binding protein 2, and nephrin down regulate the genes in Diabetic nephropathy.[38]

Nephrin and Diabetic Nephropathy

Proteinuria (microalbuminuria), is not only a biomarker for early diagnosis of diabetic nephropathy[39], but also a damaging factor to kidney, dysfunction of glomerular filtration barrier is related to the excretion of proteinuria , while nephrin plays an important role to maintain normal function of glomerular filtration barrier.[40] Some studies have described the role of nephrin protein in experimental renal diseases[41], Patari et al, has described presence of nephrin in the urine (nephrinuria) in Type I diabetes mellitus even in the absence of microalbuminuria [42] Recently, a role of nephrin in the development of diabetic nephropathy has been suggested.[43] Another study indicated that urinary nephrin is excreted in 100% of diabetics with microalbuminuria and 100% of diabetics with macroalbuminuria, as well as in 54% of diabetic patients with normoalbuminuria.[44] Analysis of UNCR (Urine Nephrin Creatinine Ratio) in large cohort studies might support the use of nephrinuria as an early biomarker for diabetic nephropathy (Figure 1). It can be hypothesized that nephrin being a part of filteration diaphragm is likely to be excreted first in case of damage to filteration barrier. In early type 2 diabetes low levels of nephrin can be detected although other currently used markers like albumin are not detected. As the disease progresses nephrin levels increases along with increase in albumin levels indicating considerable damage to the

podocytes and filtration barrier. At this stage considerable damage has already being done and therefore this further on leads to chronic renal failure. Large amount of nephrin and albumin are excreted in urine along with increase levels of urea and creatinine in blood. Early detection of nephrin might help in early diagnoses and window of time for earlier treatment in diabetic patients to slow or stop the progression of diabetic nephropathy.[45]

Figure 1. Progressive destruction of Podocyte due to diabetes leading to chronic renal failure



CONCLUSION

The structure, location and studies suggesting nephrin's role in cell to cell adhesion in podocytes and inverse association between nephrin gene expression and urinary protein excretion signify nephrin an intrusting biomarker that has good diagnostic and therapeutic potential for future research. Presence of nephrin in urine in diabetic kidney disease can offer higher sensitivity and specificity for earlier detection. Further studies are needed to evaluate the effect of increased nephrin gene expression on urinary protein excretion and progression of the disease

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