# The Role of Podocyte Cells in Diabetic Nephropathy: A Narrative Literature Review

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**A B S T R A C T**

The main cells affected in diabetic nephropathy are podocytes and proximal tubular cells. One of the main functional proteins in the podocyte slit diaphragm is podocin which podocytes need to express together with several specific proteins in the correct way for their differentiation, as well as to maintain their complex anatomy. Podocytes are highly specialized epithelial cells. They line the urinary surface of the glomerular capillary bundles. Podocytes are part of the filtration barrier along with capillary endothelial cells and GBM. Podocytes ensure selective permeability of the glomerular capillary walls. Podocin is a membrane protein with a molecular weight of 42kD which is located in the foot processes, and also forms part of the SD with the nephrin protein. Urinary podocin levels more specifically indicate ongoing glomerular damage because they were significantly increased in the normoalbuminuria group compared with the control group.

## 1. Introduction

Diabetes is the main cause of end-stage renal disease (ESRD) in 60% of patients in Malaysia, Mexico, and Singapore. Countries with an ESRD incidence of 40%–50% include Israel, Korea, Hong Kong, Taiwan, the Philippines, Japan, the US, and New Zealand. The incidence of ESRD due to diabetes is also increasing in older age groups. In 2011, the incidence rate of ESRD due to diabetes in the US was 44,266, of which 584 per million for the age groups 20-44, 45-64, and 65-74 years. Similar findings were noted in the AusDiab study of 11,247 diabetes sufferers in Australia. Nephropathy that has just occurred begins with low amounts of albuminuria, which we call microalbuminuria (persistent albuminuria at levels of 30–299 mg/24 hours). Overt nephropathy or macroalbuminuria (persistent albuminuria at levels ≥300 mg/24 hours) develops years after diagnosis. Patients who develop macroalbuminuria are more likely to develop ESRD.[1,2]

Several studies suggest that the main cells affected in diabetic nephropathy are podocytes and proximal

tubular cells. One of the main functional proteins in the podocyte slit diaphragm is podocin which podocytes need to express together with several specific proteins in the correct way for their differentiation, as well as to maintain their complex anatomy. Clinical studies have shown that a decrease in the number of glomerular podocytes is characteristic in patients with diabetic nephropathy. This decrease in podocin levels can cause the widening of the foot processes and downregulation of the podocin protein, leading to albuminuria. Many data prove that podocytes have a higher level of constitutive autophagy than other intrinsic renal cells, therefore, dysregulation of basal autophagy is believed to play an important role in podocyte injury under high glucose conditions.[3,4]

**Podocyte cells**

Podocytes are highly specialized epithelial cells. They line the urinary surface of the glomerular capillary bundles. Podocytes are part of the filtration barrier along with capillary endothelial cells and GBM. Podocytes ensure selective permeability of the glomerular capillary walls. Chronic progressive nephropathy in diabetic nephropathy is usually characterized by podocyte depletion and associated glomerulosclerosis due to oxidative stress, resulting in abnormal proteinuria, progressive kidney damage, and, ultimately, loss of kidney function. Podocytes (visceral epithelial cells) are terminally differentiated cells that line the outer surface of the glomerular capillaries. Podocytes are important functional cells in the glomerulus and cannot regenerate when injured. The main function of podocytes is to participate in the formation of the filtration barrier and to regulate glomerular filtration together with the GBM and the endothelium. Podocytes also mechanically support the glomerular vasculature and participate in the metabolic turnover of GBM and in immunological processes in the glomerulus.[5]

Podocytes are located outside the glomerular capillary loop and have a unique, complex cellular morphology consisting of a cell body, major processes,

and foot processes. The large cell bodies are located in the urinary chamber and are connected to the GBM via major processes with foot processes that extend around the circle of capillaries, forming interdigitate with other foot processes that cover the entire GBM. The cell body consists of the nucleus, mitochondria, Golgi apparatus, and endoplasmic reticulum, while the major processes consist of microtubules and vimentin intermediate filaments. Major processes branch into foot processes, which contains three different membrane segments, namely the apical area, basal area, and slit diaphragm (SD). The apical region is located on the luminal side, facing the urinary chamber. The apical region of foot processes consists of proteins, including podocalyxin, sialoglycoprotein, and podoplanin, which act as selective charges because these proteins are negatively charged. This negative charge limits the passage of negatively charged molecules such as albumin into the urinary chamber, prevents parietal cells from attaching to podocytes, and keeps adjacent podocytes apart.[6,7]

The basal foot processes area of podocytes contains several types of integrins and dystroglycans (DGs) that help attach podocytes to the glomerular basement membrane (GBM). These two major podocyte adhesion receptors ($\alpha3\beta1$-integrin and $\alpha$- $\beta$ dystroglycan) bind GBM ligands such as collagen IV, laminin, and perlecan. Both integrins and DGs associate with the actin cytoskeleton via adapter molecules. Therefore, mechanical forces can be transmitted from GBM to cytoskeleton foot processes and then to the podocyte cell body. The podocyte cytoskeleton consists of three elements: microfilaments, intermediate filaments, and microtubules. Podocyte function and architecture depend on the organization of the podocyte cytoskeleton. Podocyte cell bodies and major processes contain microtubules and intermediate filaments, while foot processes contain actin filaments. The podocyte cytoskeleton is critical for the structural integrity of the foot processes, the diaphragm silt complex with podocytes, and the GBM, as well as maintaining the mechanical strength and flexibility of podocytes. Proper regulation and reorganization of the

actin cytoskeleton in podocytes is essential for the maintenance of normal structure and function of these cells. The slit diaphragm is a special intercellular connection formed by foot processes that interact with other adjacent foot processes to form a narrow gap. The slit diaphragm is permeable to water and small molecular weight solutes but relatively impermeable to plasma proteins. The integrity of podocyte foot processes is highly dependent on SD. The slit diaphragm can be described as a multiprotein complex that regulates podocyte homeostasis and function. The proteins found in SD are nephrin, podocin, P-cadherin, mFAT-1, nephrin homologue neph-1, and related intracellular proteins such as CD2AP (CD-2-associated protein). The structural and functional integrity of GFB depends on interactions between these proteins. Proteins in SD also interact with the actin cytoskeleton, affecting podocyte motility as well as cellular signaling. Podocytes form cargo and size-selective barriers for proteins that allow permeability to molecules smaller than albumin. The functional integrity of podocytes is required to maintain the charge and size-selective barrier, maintain capillary shape, neutralize intraglomerular pressure, synthesize and maintain GBM, and production and secretion of VEGF required for glomerular endothelial cell integrity. Recent studies have confirmed the importance of podocytes in normal kidney function by showing that the function of SD as a size barrier is critical in the successful retention of albumin and other proteins.[8,9]
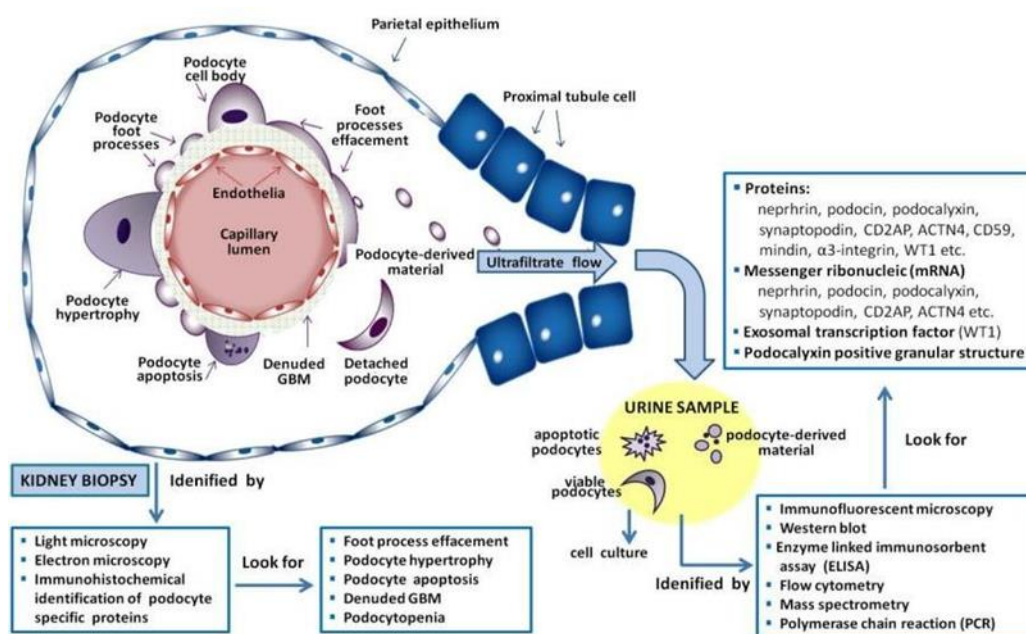


Figure 1. Podocyte injury.

**Podocyte injury in diabetic nephropathy**

Podocytes are an important cellular component in maintaining the glomerular filtration barrier, and their injury is a major determinant in the development of albuminuria and diabetic kidney disease. Podocytes are rich in mitochondria and rely heavily on them for energy to maintain normal function. Emerging evidence suggests that mitochondrial dysfunction is a key driver in the pathogenesis of podocyte injury in diabetic kidney disease. Decreased mitochondrial function results in an energy crisis, oxidative stress, inflammation, and cell death.[10]
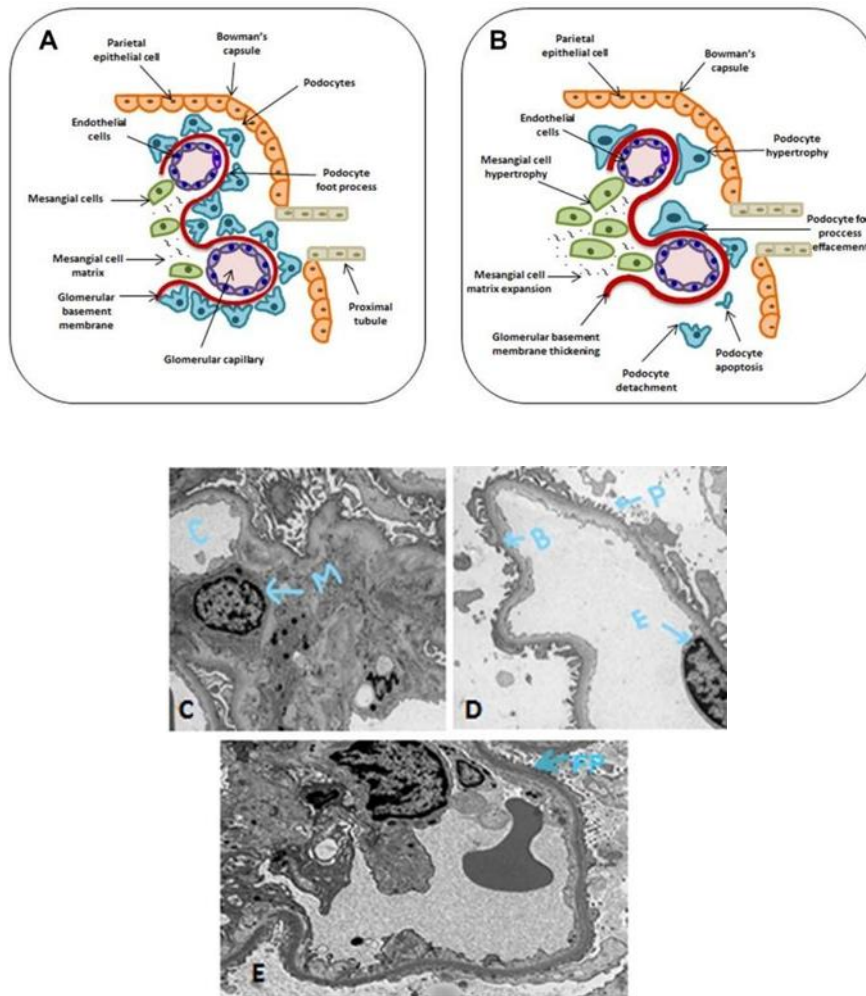
Figure 2. Illustration of glomerular structural elements. [A] Normal glomerulus; [B] glomeruli in diabetic nephropathy [C] mesangial cells (M) and glomerular capillaries (C); [D] shows the basement membrane of glomerulus B, podocytes (P) and endothelial cells (E); [E] shows deletion of podocyte foot processes in DN.

Mitochondria are major energy-producing organelles that play a central role in cell survival and death signaling. Mitochondria respond to pathophysiological cues by changing their content, fusion, fission, mitophagy, and unfolded protein responses. Hyperglycemia is the most predominant clinical abnormality in diabetes and has been viewed as one of the main risk factors for the pathogenesis of DKD.[8,9]

High glucose toxicity is mediated by many abnormal glucose metabolism pathways or signaling pathways that can lead to the overproduction of ROS and mitochondrial damage. Various studies have shown that podocytes are the first cells affected by DM, and disruption of the structural integrity of SD could be a potential site in causing podocyte injury due to hyperglycemia. Podocyte loss is believed to be one of the strongest predictors of the development of diabetic nephropathy. The importance of podocytes in maintaining renal function in diabetic nephropathy was observed through morphometric observations of renal biopsies of DM patients, which showed a significant reduction in the number of podocytes in patients with short duration of DM before the appearance of microalbuminuria or other markers of the disease.[10,11]
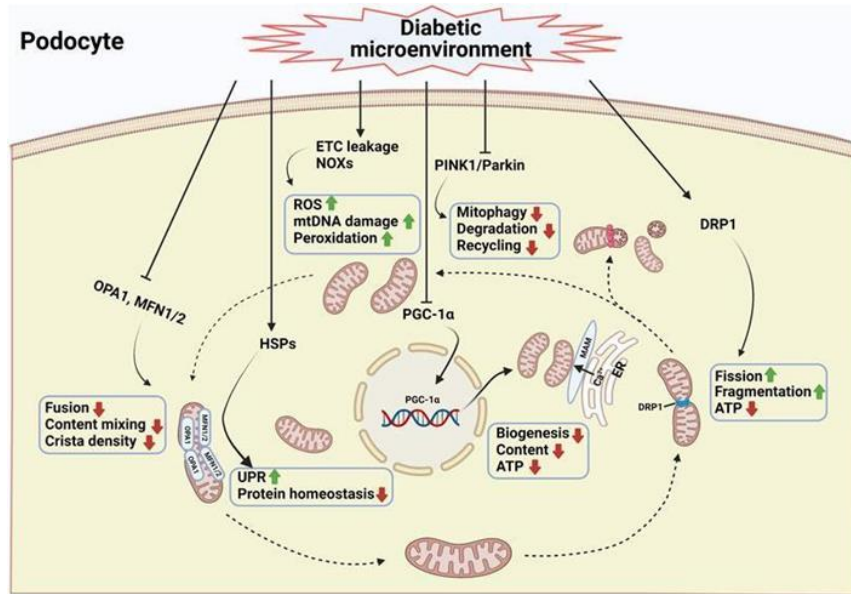
Figure 3. Podocyte mitochondrial damage during diabetic kidney disease.

Podocyte cells are sensitive to injury, and various pathogenic factors (toxic, metabolic, hemodynamic) can cause structural and functional changes in podocytes. The characteristics of podocyte injury (podocytopathy) are widening and thinning of foot processes (effacement), podocyte hypertrophy, apoptosis, podocyte detachment (release from GBM), and loss of podocytes into the urinary chamber (podocyturia) as well as a decrease in the number of podocytes in the glomeruli (podocytopenia). Podocytes require sufficient numbers to carry out their normal functions. Podocytopenia may cause proteinuria by the following mechanisms: (i) overall loss of negative charge due to an overall decrease in podocalyxin protein available to function as a charge barrier; (ii) disruption of the normal architecture of podocytes. This results in the inability of podocytes to function as a size barrier, allowing proteins and other molecules to pass unimpeded into the urine.[12]
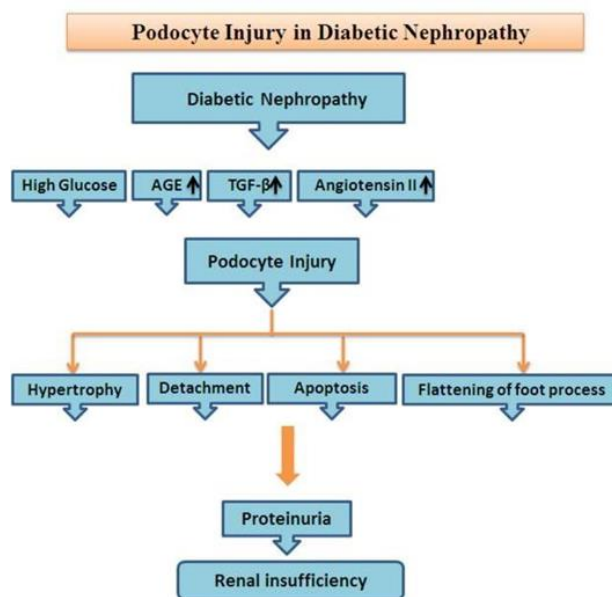


Figure 4. Podocyte injury and loss in diabetic nephropathy.

The number of podocytes is significantly reduced early in DM, and a decrease in the number of podocytes correlates with increased excretion of albuminuria and predicts the development of albuminuria. Podocytes have also been reported in 53% of the urine of DM patients with microalbuminuria and 80% of those with macroalbuminuria. High glucose is metabolized to form glucose metabolites, which directly reduce the amount of antioxidants such as glutathione, the formation of AGEs, induce PKC signaling, and disrupt RAAS. All these mechanisms are likely to increase oxidative stress by inducing NOX activation. Nicotinamide adenine dinucleotide phosphate oxidase (NADPH) induces superoxide production through oxidation in mitochondria, inflammation, and stress. NOX4 isoform is the most abundant NOX expressed in the kidney and is localized in mesangial, tubular, and podocyte cells, playing an important role in oxidative stress in kidney disease. Reactive oxygen species (ROS) formed by NADPH oxidase cause tissue damage, including injury to podocytes, and reduce podocyte density. Podocyte injury has been implicated as one of the events occurring early in ND.[13]

Two mechanisms that explain the loss of podocytes are detachment and apoptosis. Increased apoptosis is the main cause of reduced podocyte numbers, leading to proteinuria and glomerulosclerosis. Regulation of podocyte survival and death depends on the balance of pro- and anti-apoptotic factors. Podocyte apoptosis is activated by factors such as hyperglycemia, angiotensin II, angiotensin receptor 1, TGF-β1, Smad-7, ROS, detachment of GBM, mechanical tension, decrease in inhibitors that activate p27 and p21 cyclic kinases, fibroblast GF, apoptosis-inducing factor. In hyperglycemia, TGF-β1 can directly activate Smad7, which inhibits NF-κB activity and results in podocyte apoptosis. It can also stimulate p38 MAP kinase, thereby increasing Bax protein expression and producing cytochrome C, which activates the caspase-3 apoptotic pathway sequentially. Hyperglycemia also stimulates the Notch/Jag/ICN1 signaling pathway, which activates the Bcl-2 and p53 apoptotic pathways

that can induce podocyte apoptosis. Reactive oxygen species induce podocyte apoptosis through activation of proapoptotic p38 MAPK and caspase-3 in cultured podocytes and in experimental animals.[14]

Researchers have shown that TGF-β1 can induce apoptosis of cultured podocytes by stimulating p38 MAPK signaling and the classic effector caspase-3 pathway. Hyperglycemia activates the RAAS, and increased angiotensin II levels via a C-terminal Src kinase-dependent pathway have been shown to increase podocyte apoptosis.

Podocytes are a direct target of angiotensin II, causing changes in podocyte protein expression and distribution. Angiotensin II also causes podocyte injury indirectly by increasing calcium flux and ROS production. Transforming growth factor-β 1 exerts several effects on the podocytes of DM patients, namely reducing podocyte adhesion to the GBM resulting in podocyturia, inducing collagen synthesis by podocytes which results in GBM thickening, inducing epithelial-mesenchymal transition (EMT) of podocytes which results in podocyte effacement, damaging SD architecture and changing podocyte permselectivity, as well as increasing podocyte apoptosis which results in podocyte thinning. Loss of podocytes due to apoptosis triggers podocyte hypertrophy. Hypertrophy occurs because podocytes compensate for the loss of adjacent podocytes. Podocyte hypertrophy has limited effectiveness because hypertrophied podocytes must cover an increased filtration surface area, thereby reducing adhesion to the GBM and being more susceptible to existing stress conditions. There is evidence to suggest podocyte hypertrophy can be inhibited by angiotensin type I receptor blockers, suggesting a role for angiotensin II in glucose-induced podocyte hypertrophy.[15]

Podocytes can undergo a process called effacement, which is a change in the normal cellular architecture of the FP. Podocytes that experience effacement cause disturbances in: i) disruption of SD and related protein-protein interactions; ii) disruption in the normal relationship of the FP with the GBM; iii)

reorganization of the actin cytoskeleton and its associated protein-protein interactions; iv) disruption of the apical surface of the foot process which is normally negatively charged. Changes in podocyte shape are not just a passive process after injury, and they are the result of complex molecular interactions of different podocyte protein domains.[13,14]

Mutations such as those in the nephrin and podocin proteins have been shown to cause foot process effacement, indicating that the SD protein is involved in the pathogenesis effacement of the foot process. Podocytes and GBM are closely connected and prevent proteinuric excretion by preserving the GFB. Podocyte proteins such as integrins α3β1 and DGs play important roles in podocyte attachment to the GBM. Defects in α3β1 integrin and/or DGs can result in detachment and loss of podocytes.[21] Hyperglycemia can downregulate α3β1 integrin in humans and mice, and trigger its activation of integrin-linked kinase (ILK). Transforming growth factor -β1 can suppress glomerular a3b1 integrin expression, which can cause podocyte detachment. Diagnosis of podocytopathy can be made by morpho-pathological examination of kidney biopsy material (light and electron microscopy, immunohistochemical identification of podocyte-specific proteins) or by detection of podocyte proteins in urine.[15,16]

**Utilization of podocin for early screening for diabetic nephropathy**

The NPHS2 gene provides instructions for making a protein called podocin. Podocin is specifically found in cells called podocytes, where they are located in special kidney structures called glomeruli. Podocin is located on the cell surface in the area between two podocytes called the slit diaphragm. The slit diaphragm is known as a filtration barrier because it traps proteins in the blood so they remain in the body while allowing other molecules, such as sugar and salt, to be excreted in the urine. Podocin is a membrane protein with a molecular weight of 42kD, which is located in the foot processes and also forms part of the SD with the nephrin protein. Podocin is a

membrane protein of the stomatin protein family consisting of 383 amino acids. Podocin has a hairpin-like structure. Podocin interacts with the transmembrane protein nephrin and the CD2AP protein via the COOH terminus. These interactions play an important role in maintaining SD structure and function and facilitating signaling.[17]

Podocin likely helps carry other proteins required for a functional slit diaphragm to the cell surface of podocytes. The protein is also involved with podocyte cell signaling, helping the cells adapt to changes that occur during the filtration process. The direct interaction of podocin with nephrin is enhanced after nephrin phosphorylation. These findings suggest that podocin may play a role in stabilizing nephrin in SD and facilitating signaling. One of the factors that influence podocyte function in DM is the proteins in SD including podocin protein and other proteins. Podocin also interacts with another SD protein that has a structure similar to nephrin, namely Neph1. The podocin-Neph1 interaction is believed to be important for the recruitment of nephrin to lipid raft which augments nephrin signaling.[18]

Podocin dysfunction causes altered SD assembly and proteinuria in experimental models. This protein is encoded by the NPHS2 gene, which is composed of eight exons and is located on chromosome 1q25-q31. Genetic defects in NPHS2 can cause nephrotic syndrome. NPHS2 gene mutations are found in congenital steroid-resistant nephrotic syndrome and sporadic steroid-resistant nephrotic syndrome, indicating that podocin plays an important role in maintaining podocyte structure and SD integrity, so that podocin plays an important role in the pathogenesis of proteinuria.[13,14]

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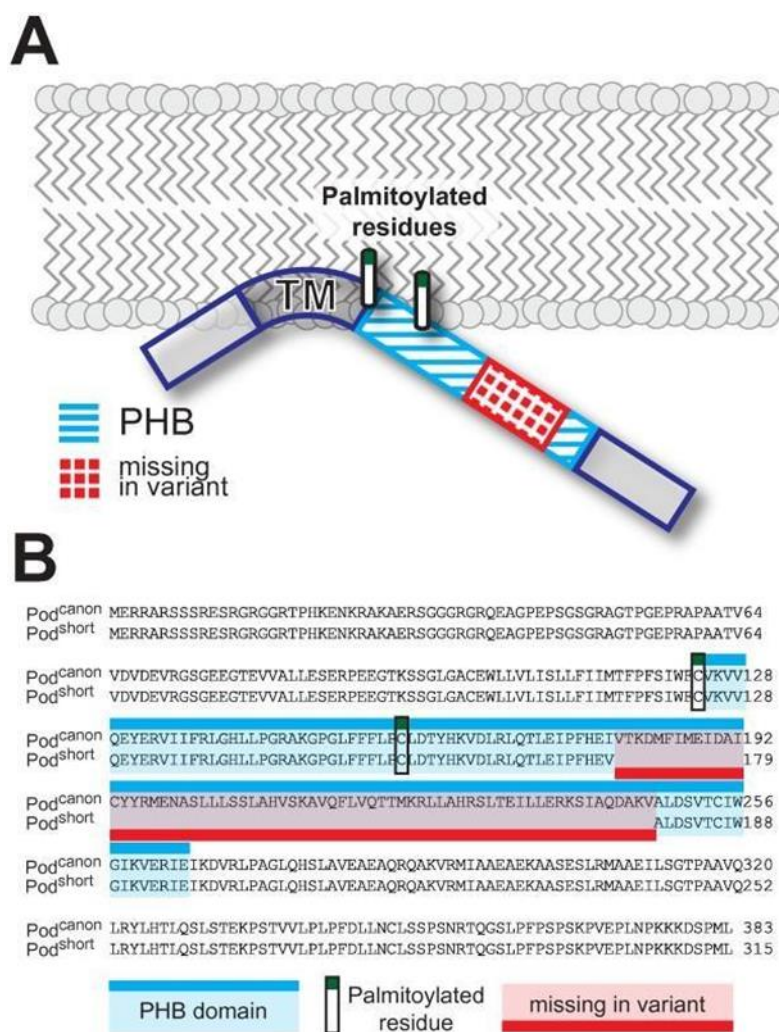
Figure 5. Schematic review and alignment of podocin short isoforms. A) Schematic drawing of podocin with the differences between the two isoforms shown. Most of the PHB domain is lost in the short isoform. B) Sequence alignment of the two human podocin isoforms.

Clinical studies show that reduced glomerular podocyte levels are characteristic in patients with diabetic nephropathy. This decrease can cause dilation in the foot process and upregulation of the podocin protein, leading to marked albuminuria. Many data prove that podocytes have a higher level of constitutive autophagy than other intrinsic renal cells, so dysregulation of basal autophagy is believed to play an important role in podocyte injury under high glucose conditions.[12,13]

Podocin was excreted in the urine at higher concentrations among patients with albumin-creatinine ratio (ACR) <30, ACR 30-299, and ACR >300, respectively, compared with healthy controls (p < 0.001). Glomerular filtration rate showed a significant negative correlation with podocin levels excreted in urine, whereas urinary podocin was positively correlated with fasting blood sugar, postprandial sugar, glycosylated hemoglobin, triglyceride levels and duration of diabetes along with systolic and diastolic blood pressure, body mass index, microalbumin, and urine albumin-creatinine ratio. Podocin ROC curve analysis in the study showed a sensitivity of 98.75% and a specificity of 98.89% for detecting nephropathy in normoalbuminuric diabetes patients in level cut off 18,5 ng/ml. It proved that urinary podocin is not only an early biomarker but is sensitive and specific for predicting the onset of

nephropathy among normoalbuminuric diabetes patients. This study supports urinary podocin as a highly sensitive and specific marker for predicting diabetic nephropathy.[14,15]

The study showed that there was a statistically significant difference between all groups studied regarding urinary podocin levels (P < 0.001). Urinary podocin appeared even in the normoalbuminuria group (9.2 [7.1 – 12] ng/ml), which was significantly higher compared to controls (median 3.9 [2.2 – 4.8] ng/ml), and significantly higher levels were found in the macroalbuminuria group (median 41.5 [38.5 – 48.5] ng/ml) compared with the other groups. This can be explained because diabetes is associated with damage to the GFB glomerular filtration barrier and exposes podocytes to detrimental factors through several mechanisms, such as neurohormonal changes, oxidative stress, and reduced expression of adhesion molecules. This condition can result in injury and loss of podocytes, leading to increased glomerular permeability, which is manifested clinically as albuminuria.[19]

Urinary podocin may be an additional tool for nephrologists to consider to assess glomerulopathy activity. The study also showed a very significant positive correlation between the duration of diabetes and urinary podocin levels because the longer the duration of diabetes, the greater the urinary podocin levels, with a P value <0.001. The sensitivity of urinary podocin as an early marker for predicting diabetic nephropathy in the normoalbuminuria group (versus controls) was 94.7%, while the specificity was 92%, with a positive predictive value (NPP) of 94.7 and a negative predictive value (NPN) of 92% in cut off >6.0 ng/ml (p <0.001). These findings suggest that it is a highly sensitive and specific marker for predicting diabetic nephropathy.[20]

## 2. Conclusion

Podocytes are highly specialized epithelial cells. They line the urinary surface of the glomerular capillary bundles. Podocytes are part of the filtration barrier along with capillary endothelial cells and GBM.

Podocytes ensure selective permeability of the glomerular capillary walls. Podocin is a membrane protein with a molecular weight of 42kD, which is located in the foot processes and also forms part of the SD with the nephrin protein. Urinary podocin levels more specifically indicate ongoing glomerular damage because they were significantly increased in the normoalbuminuria group compared with the control group.

## 3. References

1. Bobkova I, Chebotareva N, Schukina A, Kamyshova E, Bobrova L. New insights into the molecular mechanisms of podocytes injury in diabetes. J Clin Exp Nephrol. 2018; 3(3): 17.

2. Liu S, Yuan Y, Xue Y, Xing C, Zhang B. Podocyte injury in diabetic kidney disease: a focus on mitochondrial dysfunction. Frontiers in Cell and Developmental Biology. 2022; 10.

3. Bose M, Almas S, Prabhakar S. Wnt signaling and podocyte dysfunction in diabetic nephropathy. J Investig Med. 2017; 65(8): 1093–101.

4. Dai H, Liu Q, Liu B. Research progress on mechanism of podocyte depletion in diabetic nephropathy. J Diabetes Res. 2017; 2017.

5. Yu SM-W, Nissaisorakarn P, Husain I, Jim B. Proteinuric kidney diseases: a podocyte's slit diaphragm and cytoskeleton approach. Front Med. 2018; 5: 221.

6. Mukhi D, Nishad R, Menon RK, Pasupulati AK. Novel actions of growth hormone in podocytes: implications for diabetic nephropathy. Front Med. 2017; 4: 102.

7. Podgórski P, Konieczny A, Lis Ł, Witkiewicz W, Hruby Z. Glomerular podocytes in diabetic renal disease. Adv Clin Exp Med Off organ Wroclaw Med Univ. 2019; 28(12): 1711–5.

8. ElShaarawy A, Abdelmoneim Behairy M, Abdelhameed Bawady S, Abdelsattar HA, Shadad E. Urinary podocin level as a predictor of diabetic kidney disease. J Nephropathol. 2019; 8(3).

9. Völker L, Schurek E-M, Rinschen M, Tax J, Schutte B, Lamkemeyer T, et al. Characterization of a short isoform of the kidney protein podocin in human kidney. BMC Nephrol. 2013; 14: 102.

10. El-Shazly AAA, Sallam AM, El-Hefnawy MH, El-Mesallamy HO. Epidermal growth factor receptor and podocin predict nephropathy progression in type 2 diabetic patients through interaction with the autophagy influencer ULK-1. J Diabetes Complications. 2019; 33(2): 128–33.

11. Kondapi K, Silambanan S, Moorthy S, Kumar NL. A study of the risk factors and urinary podocin as an early prognostic indicator of renal injury in diabetic nephropathy. J Assoc Physicians India. 2021;69(6):11–2.

12. Kishore MK, Silambanan DS, Moorthy DS. Diagnostic sensitivity of biomarkers in assessing the occurrence and progression of diabetic nephropathy. Eur J Mol Clin Med. 2021; 8(3): 1554–71.

13. Hayman SR, Calle JC, Jatoi A, Craici IM, Wagner SJ, Weaver AL, et al. Urinary podocyte excretion and proteinuria in patients treated with antivascular endothelial growth factor therapy for solid tumor malignancies. Oncology. 2014; 86(5–6): 271–8.

14. Zeng L, Fung WW-S, Chan GC-K, Ng JK-C, Chow K-M, Szeto C-C. Urinary and kidney podocalyxin and podocin levels in diabetic kidney disease: a kidney biopsy study. Kidney Med. 2023; 5(1): 100569.

15. Eknoyan G, Lameire N, Wheeler DC. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. Kidney International. Kidney Int Suppl. 2022; 1-127.

16. Lim AK. Diabetic nephropathy - complications and treatment. Int J Nephrol Renovasc Dis. 2014; 7: 361–81.

17. Umanath K, Lewis JB. Update on diabetic nephropathy: core curriculum 2018. Am J Kidney Dis Off J Natl Kidney Found. 2018; 71(6): 884–95.

18. Ahmed SS. Update on diagnosis and management of early-stage diabetic kidney disease. Am J Med Sci. 2019; 9(3): 114–24.

19. Doshi SM, Friedman AN. Diagnosis and management of type 2 diabetic kidney disease. Clin J Am Soc Nephrol. 2017;12(8): 1366–73.

20. Valverde MG, Mille LS, Figler KP, Cervantes E, Li VY, Bonventre JV, et al. Biomimetic models of the glomerulus. Nat Rev Nephrol. 2022; 18(4): 241– 57.