

Podocytes Play Critical Role in Nephropathy

Pathophysiological changes to these renal cells may cause progression to this diabetic microvascular complication.

BY FUAD N. ZIYADEH, MD

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are common treatments for diabetic nephropathy, however, there is a need to develop more effective therapies.

Promising new treatments may target the roles of such proteins as transforming growth factor-beta (TGF-beta) and vascular endothelial growth factor (VEGF) in the development of diabetic kidney disease. Antibodies or inhibitors of these growth factors are gaining importance due to their ability to protect kidney cells.

While alterations of glomerular mesangial cells have traditionally been the focus of research in diabetic kidney disease, injury of podocytes has recently been recognized as an important early step in the development and progression of diabetic nephropathy.¹ In a preclinical model of type 2 diabetes, damage to these renal cells was the origination of nephropathy.²

Podocytes consist of thick extensions that envelop glomerular capillary loops³ and line the glomerular basement membrane (GBM) that filters the blood into the urinary space of the glomerulus.⁴⁻⁶ In between empty spaces that are 30 nm to 40 nm in length are slit diaphragms that contain nephrin. These bridge the space between adjacent podocytes and are only permeable to water and small solutes.^{7,8}

Damaged podocytes may contribute to the development of diabetic nephropathy (Figure 1).⁹ One example of this is the increase in the width of the foot processes, which may occur in patients with type 1 diabetes with microalbuminuria. Berg et al¹⁰ found an association between the width of foot process and urinary albumin excretion (UAE) rate.

Another noticeable change in diabetic nephropathy patients is the reduction of the number or density of podocytes (podocytopenia). Various studies have noted this change both type 1 and type 2 diabetes patients.¹¹⁻¹⁴ Meyer et al¹⁵ reported that the strongest predictor of

progressive renal disease in a population of type 2 diabetic Pima Indians was the decrease of podocytes in the glomerulus. The most rapid progression of renal disease was noted in type 2 diabetes patients with the greatest podocyte loss. Podocyte density predicts albuminuria.¹⁴

There is not enough evidence to suggest the exact cause of podocyte loss in diabetic patients, however, two hypotheses – apoptosis and cell detachment – are under investigation. When intraglomerular activity of TGF-beta is increased, it causes apoptosis.¹⁶ Apoptosis may share a role in the development of diabetic nephropathy.¹⁷⁻²⁰ Another reasoning is that the detachment from the GBM may cause the loss of podocytes. Vogemann et al²¹ found that as podocytes became detached, they were discarded into urine as live cells.

The slit diaphragm has permselective properties⁹ that may become disturbed due to widening of the foot processes and the decreased length of the slit diaphragm. Proteinuria ensues due to these structural changes and the altered macromolecular composition of the GBM. As this occurs, glomerular filtration rate may be lowered. This is made worse by glomerulosclerosis. Heavy proteinuria may

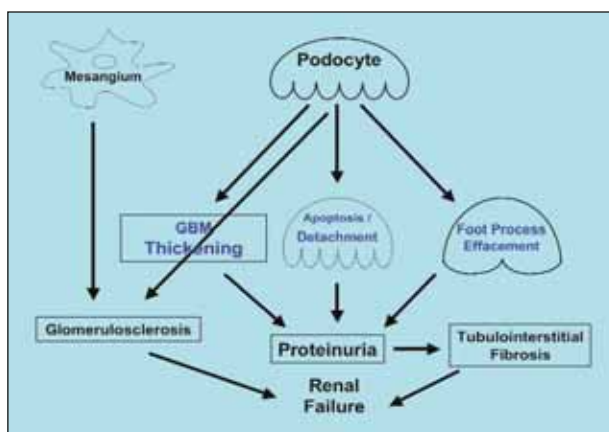
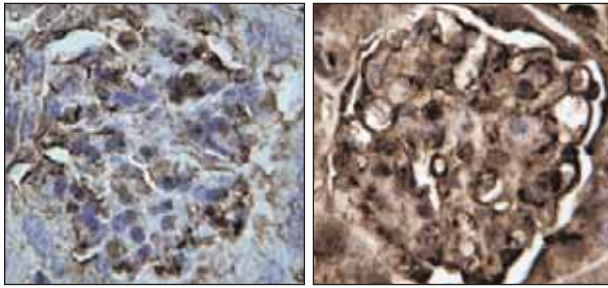


Figure 1. Podocytes that become damaged may contribute to the development of diabetic nephropathy.



Figures 2, 3: (Left) VEGF₁₆₄ protein level is increased in the streptozotocin-induced db/m nondiabetic. (Right) The level is also increased in the db/db diabetic mouse.

promote the development of tubular atrophy and interstitial fibrosis. Occurring in combination with glomerulosclerosis, these structural changes may cause progression to chronic renal insufficiency.¹⁸

RESTORE NEPHRIN

ACE inhibitors and ARBs have beneficial effects on podocytes including protection from podocyte loss and/or damage. A decreased number of urinary podocytes²² and restoration of nephrin protein expression to near-normal levels²³ are seen with use of an ACE inhibitor or ARB. One reason that the width of foot process increases is because nephrin, which is crucial in protecting podocyte integrity, is decreased.²⁴ Several studies showed a downregulation in nephrin protein production in patients with diabetes versus those with nondiabetes.^{23,25,26}

In addition to the downregulation of nephrin, other pathophysiological changes affect diabetic nephropathy. The increase of podocyte-derived VEGF caused proteinuria in type 1 and 2 diabetes (Figures 2, 3).^{27,28} In these studies, one in type 1 streptozotocin-induced diabetic rats and another in type 2 diabetic db/db mice, UAE rate dropped by 50% in anti-VEGF-antibody-treated diabetic mice as compared with untreated diabetic mice. Podocytes not only produce VEGF, they also respond to its presence through specific receptors.^{29,30}

Intraglomerular TGF-beta activity is likely to occur in patients with diabetes, and it contributes significantly to matrix accumulation by glomerular mesangial cells and the development of glomerulosclerosis. The increase of TGF-beta activity may also cause apoptosis and/or podocytes to become detached, which as mentioned above are suggested causes of podocyte loss in patients with diabetes.³¹⁻³³

Curiously, and unlike other renal cell types, the podocyte does not increase TGF-beta expression as a response to diabetes.

In patients with diabetes, many pathophysiological changes occur in podocytes, and they effect the progres-

sion of diabetic nephropathy. How these cells respond to diabetes may also increase progression of the disease.

Treatment with an ACE inhibitor or ARB has provided some relief, however, future treatments that offer extensive protection of the podocyte may further prevent the development and progression of diabetic nephropathy. ■

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1. Wolf G, Chen S, Ziyadeh FN. From the periphery of the glomerular capillary wall toward the center of disease: Podocyte injury comes of age in diabetic nephropathy. *Diabetes*. 2005;54:1626-1634.
2. Coimbra TM, Janssen U, Grone HJ, et al. Early events leading to renal injury in obese Zucker (fatty) rats with type II diabetes. *Kidney Int*. 2000;57:167-182.
3. Kerjaschi D. Caught flat-footed: podocyte damage and the molecular bases of focal glomerulosclerosis. *J Clin Invest*. 2001;108:1583-1587.
4. Tsilibary EC. Microvascular basement membranes in diabetes mellitus. *J Pathol*. 2003;200:537-546.
5. Kretzler M. Regulation of adhesive interaction between podocytes and glomerular basement membrane. *Microsc Res Tech*. 2002;57:247-253.
6. Kojima K, Kerjaschi D. Is podocyte shape controlled by the dystroglycan complex? *Nephrol Dial Transplant*. 2002;17(suppl) 9:23-24.
7. Tryggvason K. Unraveling the mechanisms of glomerular ultrafiltration: nephrin, a key component of the slit diaphragm. *J Am Soc Nephrol*. 1999;10:2440-2445.
8. Wariloaara J, Olverstedt LG, Khoshnoodi J, et al. Nephrin strands contribute to a porous slit diaphragm scaffold as revealed by electron tomography. *J Clin Invest*. 2004;114:1475-1483.
9. Pavenstadt H, Kriz W, Kretzler M. Cell biology of the glomerular podocyte. *Physiol Rev*. 2003;83:253-307.
10. Berg UB, Torbjomsdotter TB, Jaremo G, et al. Kidney morphological changes in relation to long-term renal function and metabolic control in adolescents with IDDM. *Diabetologia*. 1998;41:1047-1056.
11. Steffes MW, Schmidt D, McCrey R, Basgen JM. Glomerular cell number in normal subjects and in type 1 diabetic patients. *Kidney Int*. 2001;59:2104-2113.
12. Pagtalunan ME, Miller PL, Jumping-Eagle S, et al. Podocyte loss and progressive glomerular injury in type II diabetes. *J Clin Invest*. 1997;99:342-348.
13. White KE, Bilous RW, Marshall SM, et al. Podocyte number in normotensive type 1 diabetic patients with albuminuria. *Diabetes*. 2002;51:3083-3089.
14. Dalla Vestra M, Masiero A, Roiter AM, et al. Is podocyte injury relevant in diabetic nephropathy? Studies in patients with type 2 diabetes. *Diabetes*. 2003;52:1031-1035.
15. Meyer TW, Bennett GL, Nelson RG. Podocyte number predicts long-term urinary albumin excretion in Pima Indians with type II diabetes and microalbuminuria. *Diabetologia*. 1999;42:1341-1344.
16. Yoo J, Ghiassi M, Jirmanova L, et al. Transforming growth factor-beta-induced apoptosis is mediated by Smad-dependent expression of GADD45b through p38 activation. *J Biol Chem*. 2003;278:43001-43007.
17. Ortiz A, Ziyadeh FN, Neilson EG. Expression of apoptosis-regulatory genes in renal proximal tubular epithelial cells exposed to high ambient glucose and in diabetic kidneys. *J Invest Med*. 1997;45:50-56.
18. Murata I, Takemura G, Asano K, et al. Apoptotic cell loss following cell proliferation in renal glomeruli of Otsuka Long-Evans Tokushima Fatty rats, a model of human type 2 diabetes. *Am J Nephrol*. 2002;587-595.
19. Kumar D, Robertson S, Burns KD. Evidence of apoptosis in human diabetic kidney. *Mol Cell Biochem*. 2004;259:67-70.
20. Vogelmann SU, Nelson WJ, Myers BD, et al. Urinary excretion of viable podocytes in health and renal disease. *Am J Physiol Renal Physiol*. 2003;285:F40-F48.
21. Remuzzi G, Bertani T. Pathophysiology of progressive nephropathies. *N Engl J Med*. 1998;339:1448-1456.
22. Nakamura T, Ushiyama C, Suzuki S, et al. Urinary excretion of podocytes in patients with diabetic nephropathy. *Nephrol Dial Transplant*. 2000;15:1379-1383.
23. Langham RG, Kely DJ, Cox AJ, et al. Proteinuria and the expression of the podocyte slit diaphragm protein, nephrin, in diabetic nephropathy: effects of angiotensin converting enzyme inhibition. *Diabetologia*. 2002;45:1572-1576.
24. Toyoda M, Suzuki D, Umezono T, et al. Expression of human nephrin mRNA in diabetic nephropathy. *Nephrol Dial Transplant*. 2004;19:380-385.
25. Koop K, Elkmans M, Baelde HJ, et al. Expression of podocyte-associated molecules in acquired human kidney diseases. *J Am Soc Nephrol*. 2003;14:2063-2071.
26. Benigni A, Gagliardini E, Tomasoni S, et al. Selective impairment of gene expression and assembly of nephrin in human diabetic nephropathy. *Kidney Int*. 2004;65:2193-2200.
27. De Vriese AS, Tilton RG, Elger M, et al. Antibodies against vascular endothelial growth factor improve early renal dysfunction in experimental diabetes. *J Am Soc Nephrol*. 2001;12:993-1000.
28. Flyvbjerg A, Dagnaes-Hansen F, De Vriese AS, et al. Amelioration of long-term renal changes in obese type 2 diabetic mice by a neutralizing vascular endothelial growth factor antibody. *Diabetes*. 2002;51:3090-3094.
29. Chen S, Kasama Y, Lee JS, et al. Podocyte-derived vascular endothelial growth factor mediates the stimulation of alpha3(IV) collagen production by transforming growth factor-beta1 in mouse podocytes. *Diabetes*. 2004;53:2939-2949.
30. Foster RR, Hole R, Anderson K, et al. Functional evidence that vascular endothelial growth factor may act as an autocrine factor on human podocytes. *Am J Physiol Renal Physiol*. 2003;284:F1263-F1273.
31. Ding G, Reddy K, Kapasi AA, et al. Angiotensin II induces apoptosis in rat glomerular epithelial cells. *Am J Physiol Renal Physiol*. 2002;283:F173-F180.
32. Schiffer M, Mundel P, Shaw AS, et al. A novel role for the adaptor molecule CD2-associated protein in transforming growth factor-beta-induced apoptosis. *J Biol Chem*. 2004;279:37004-37012.
33. Chen HC, Chen CA, Guh HY, et al. Altering expression of alpha3beta1 integrin on podocytes of human and rats with diabetes. *Life Sci*. 2000;67:2345-2353.