Podocytes Play Critical Role in Nephropathy

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

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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. In a preclinical model of type 2 diabetes, damage to these renal cells was the origination of nephropathy.

Podocytes consist of thick extensions that envelop glomerular capillary loops and line the glomerular basement membrane (GBM) that filters the blood into the urinary space of the glomerulus. 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.

Damaged podocytes may contribute to the development of diabetic nephropathy (Figure 1). 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 al 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 in the number or density of podocytes (podocytopenia). Various studies have noted this change both type 1 and type 2 diabetes patients.

Meyer et al 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.

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. Apoptosis may share a role in the development of diabetic nephropathy. Another reasoning is that the detachment from the GBM may cause the loss of podocytes. Vogemann et al found that as podocytes became detached, they were discarded into urine as live cells.

The slit diaphragm has permselective properties 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 lead to a reduction in glomerular filtration rate (GFR) and eventually to renal failure.

Figure 1. Podocytes that become damaged may contribute to the development of diabetic nephropathy.
promote the development of tubular atrophy and interstitial fibrosis. Occurring in combination with glomerulosclerosis, these structural changes may cause progression to chronic renal insufficiency.28

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-

diabetes 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.