

# Molecular Mechanism of Diabetic Nephropathy

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## Brief Report

Diabetic nephropathy is a prominent cause of end-stage renal failure, which may explain diabetes-related impairments and high mortality rates. Diabetic nephropathy appears to be caused by a combination of metabolic and hemodynamic variables, which activate similar pathways that cause kidney damage. Recent major landmark clinical trials have revealed that strict glucose control lowers the risk of diabetic nephropathy development and progression, and that blocking the renin-angiotensin system (RAS) is a key target for both metabolic and hemodynamic derangements in diabetic nephropathy. Diabetic nephropathy, on the other hand, continues to be the major cause of end-stage renal failure in affluent countries. As a result, developing novel therapeutic techniques that directly target diabetic nephropathy could be beneficial for the majority of diabetic patients. High glucose elicits vascular inflammation and changes gene expression of growth factors and cytokines through various mechanisms such as increased production of oxidative stress and advanced glycation end products (AGEs) and activation of the RAS and protein kinase C (PKC), which may be involved in the development and progression of diabetic nephropathy. Diabetic nephropathy appears to be caused by a combination of metabolic and hemodynamic variables, which activate similar pathways that cause kidney damage. Recent large prospective clinical trials have revealed that strict glucose control significantly lowers microvascular problems in diabetic patients, and the Renin-angiotensin System (RAS) is a key target for both metabolic and hemodynamic abnormalities in diabetic nephropathy [1].

For diabetic nephropathy patients, innovative treatment methods that particularly address these metabolic and hemodynamic derangements are desired. In individuals with diabetes and/or end-stage renal failure, advanced glycation end products (AGEs) are heterogeneous cross-linked sugar-derived proteins that can accumulate in the glomerular basement membrane, mesangial cells, endothelial cells, and podocytes. Multifactorial mechanisms such as oxidative stress generation and overproduction of different growth factors and cytokines are thought to be involved in the pathogenesis of diabetic nephropathy. Furthermore, it has recently been postulated that the crosstalk between AGEs and the renin-angiotensin system (RAS) plays a role in diabetic nephropathy [2].

Furthermore, activation of the RAS causes the creation of Reactive Oxygen Species (ROS), which stimulates the synthesis of growth factors and cytokines by renal cells. These findings suggest that combining RAS inhibitors with blockers of AGE formation and/or their downstream pathway could be a novel therapeutic option for diabetic nephropathy prevention. NAD(P)H oxidase, advanced glycation end products (AGE), abnormalities in the polyol pathway, uncoupled Nitric Oxide Synthase (NOS), and the mitochondrial respiratory chain via oxidative phosphorylation have all been linked to increased production of reactive oxygen species (ROS). Excess ROS influence protein kinase C, mitogen-activated protein kinases, and different cytokines and transcription factors, resulting in increased expression of Extracellular Matrix (ECM) genes as fibrosis and end-stage renal disease develop. NAD(P)H oxidase, advanced

glycation end products (AGE), abnormalities in the polyol pathway, uncoupled Nitric Oxide Synthase (NOS), and the mitochondrial respiratory chain via oxidative phosphorylation have all been linked to increased production of Reactive Oxygen Species (ROS) [3-4].

Excess ROS influence protein kinase C, mitogen-activated protein kinases, and different cytokines and transcription factors, resulting in increased expression of extracellular matrix (ECM) genes as fibrosis and end-stage renal disease develop. TGF-1 (transforming growth factor-1) de novo synthesis is induced, and TGF-1 appears to be involved because blocking this pro-sclerotic factor inhibits high glucose-induced collagen synthesis. It was discovered that angiotensin II promotes TGF-1 synthesis as well, probably through the same signal transduction route. In addition to the traditional clinical chemistry criteria for assessing renal function, urine albumin excretion is now frequently employed to detect the onset of diabetic nephropathy. Tubular marker proteins may be utilized to detect early renal impairment since diabetes produces glomerular and tubular alterations. In early diabetic nephropathy, urine excretion of matrix proteins (e.g., collagen) and cytokines (e.g., TGF-1) was observed to be higher.

## Role of Reactive Oxygen Species (ROS)

In mesangial and tubular epithelial cells, high glucose levels cause intracellular reactive oxygen species (ROS). Inhibition of protein kinase C (PKC), NADPH oxidase, and mitochondrial electron transfer chain complex I efficiently blocks high glucose-induced ROS creation in mesangial cells, suggesting that PKC, NADPH oxidase, and mitochondrial metabolism all play a role in high glucose-induced ROS generation. Advanced glycation end products, TGF-beta-1, and angiotensin II can all cause ROS production and amplify high glucose-activated signaling in the diabetic kidney. Both high glucose and reactive oxygen species (ROS) activate the signal transduction cascade (PKC, mitogen-activated protein kinases, and Janus kinase/signal transducers and activators of transcription) and transcription factors (nuclear factor-kappa B, activated protein-1, and specificity protein-1), upregulating TGF-beta-1 and ECM genes and proteins. These findings imply that in diabetic kidneys, ROS function as intracellular messengers and glucose signaling molecules. In the development of diabetic nephropathy, reactive oxygen species (ROS) play a larger role. Future research into other ROS-activated downstream signaling pathways in mesangial and other renal cells will help us better understand the final cellular responses to HG, such as proliferation, differentiation, apoptosis, and ECM buildup. This will allow for the development of more sensible diabetic nephropathy treatment options [5].

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