

# Agents in Development for the Treatment of Diabetic Nephropathy

Newer targets, some of which are linked to glucose-dependent pathways, appear to be a major focus of new treatments directed against the development of renal damage as a result of diabetes.

REVIEWED BY KEI FUKAMI, MD

**D**iabetic nephropathy is a leading cause of end stage renal disease and accounts for significant morbidity and mortality in patients with diabetes. Writing in *Expert Opinion on Investigational Drugs*, Kei Fukami, MD, and colleagues said that diabetic nephropathy seems to occur as a result of an interaction between metabolic and hemodynamic factors, which activate common pathways that lead to renal damage.

“Several large studies, particularly the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS), have shown the beneficial effects of intensive metabolic control and antihypertensive treatment on the development of diabetic nephropathy,” they wrote. Dr. Fukami is from the Danielle Alberti Memorial Centre for Diabetes Complications, Baker Heart Research Institute in Melbourne, Australia.

Most treatments of the past have focused on the control of hyperglycemia. The major focus of newer treatments, however, seem to be on newer targets, some of which are linked to glucose-dependent pathways and are directed against the development and progression of renal damage as a result of diabetes. “It is anticipated that additional therapeutic approaches that inhibit both metabolic and hemodynamic pathways will include strategies that target growth factors, cytokines and intracellular second messengers,” Dr. Fukami wrote (Figure 1). Such an approach is expected to lead to improved therapies for the treatment of diabetic nephropathy.

## TARGETING METABOLIC PATHWAYS

Current strategies that treat diabetes by reducing hyperglycemia include reducing insulin resistance with glitazones and supplementing native insulin with exogenous insulin, Dr. Fukami and colleagues said. Over the last few years, sev-

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eral new agents have been described as insulin sensitizers. It is predicted that these approaches will confer end-organ protection because of their ability to reduce plasma glucose levels.

**Inhibition of advanced glycation.** Advanced glycation end products (AGEs) in the kidney occur at an accelerated rate in diabetic patients due to chronic hyperglycemia, Dr. Fukami wrote. The accumulation of AGEs along with other substances leads to alteration in renal architecture and the loss of renal function.

## TREAT DEVELOPMENT, PROGRESSION

Drugs that inhibit the formation of AGEs include aminoguanidine (AG), ALT-946, pyridoxamine and OPB-9195. AG was the first of its type to treat the development and progression of diabetic nephropathy. Pimagedine (AG HCl), though effective in clinical trials, overall proved too toxic in the clinical setting. ALT-946 is a newer, more selective inhibitor of AGE. Dr. Fukami and colleagues found it prevented glomerular AGE accumulation and albuminuria in streptozotocin (STZ)-induced diabetic rats. Pyridoxamine is a natural intermediate of vitamin B6 metabolism, which has been shown to reduce AGE levels and improve renal and vascular dysfunction in the type 1 STZ diabetic model. It is in phase 2 clinical trials for type 1 and 2 diabetes. OPB-9195 is a thiazolidine derivative. It has been reported to inhibit the formation of AGEs, prevent diabetic nephropathy and significantly pre-

vent sclerotic changes, but with no effect on blood glucose, Dr. Fukami said.

Novel AGE formation inhibitors include LR-90, metformin and benfotiamine. LR-90 is a newly recognized AGE inhibitor that acts similarly to AG and pyridoxamine. Metformin has been shown to reduce diabetes-associated vascular risk in clinical studies. Additional trials are needed to confirm its role in diabetic nephropathy. Benfotiamine is a lipid-soluble thiamine derivative that shows great promise, according to Dr. Fukami. "Studies have recently demonstrated that benfotiamine is able to block major biochemical pathways implicated in the pathogenesis of diabetic complications, including the accumulation of AGEs." Several trials are either in progress or in development.

ALT-711 is an AGE crosslink breaker. These compounds

The development of new therapies for diabetic neuropathy may help reverse the progression of renal dysfunction.

have been shown to have effects on the vasculature in diabetes and have improved arterial compliance in aged humans, Dr. Fukami and colleagues reported. "Our group has demonstrated that ALT-711 treatment of STZ-induced diabetic rats ameliorates diabetes-associated increases in serum and tissue AGEs in association with reduced albumin excretion rate, blood pressure, renal collagen, tubulointerstitial area and glomerulosclerotic index." This compound is under evaluation in different phase 2 clinical trials. Future studies of this compound are warranted, they wrote.

### REDUCE ENDOGENOUS ACTIVATION

Another approach to AGE reduction is to provide soluble receptors to compete with the cellular receptors for AGEs (RAGEs), thereby reducing endogenous activation. Several studies have shown that this is possible, although it may be difficult to translate clinically, the investigators wrote.

**Inhibition of the polyol pathway.** The polyol pathway has been investigated as a player in the pathogenesis of diabetic nephropathy. Aldose reductase (AR) and sorbitol dehydrogenase are part of the pathway. AR inhibition attenuates hyperfiltration in normoalbuminuria and prevents the course of microalbuminuria in type 1 diabetic patients, Dr. Fukami and researchers said. AR inhibitors have been studied, such as zopolrestat, minarestat, zenarestat and epalrestat.

**Antioxidant treatment.** Oxidative stress is recognized to have a crucial role in the pathogenesis of diabetic complications. It is believed that agents that normalize mitochondri-

al reactive oxygen species could be useful in the progression of diabetic nephropathy, although it has not been directly tested.

**Modulation of glucose transporters.** Reports claim that the first step of glucose signaling is its transport into the cells through the glucose transporter, specifically brain-type glucose transporter-1 (GLUT-1). Ultimately, through various chemical expressions in diabetic patients, there is an increase in GLUT-1 expression leading to pathogenesis and progression of diabetic nephropathy. Modulation of this mechanism through an agent known as an SGLT2 inhibitor may be effective in diabetic nephropathy.

**Glycosaminoglycan treatment.** Dr. Fukami and coauthors said that glycosaminoglycans are thought to be important to glomerular basement membrane permeability. Modulation of this may play a role in diabetic nephropathy and a compound is being studied in phase 2 and 3 clinical trials.

### TARGETING HEMODYNAMIC PATHWAYS

**Renin-angiotensin system blockade.** Control of blood pressure and blockade of the renin-angiotensin system (RAS) has a major effect on reducing proteinuria and slowing progression to renal failure in type 1 and type 2 diabetes, according to numerous studies. Antihypertensive agents such as AT1 and angiotensin-converting enzyme (ACE) inhibitors efficacy has been shown in clinical trials. The role of AT2 remains to be clarified in further study, Dr. Fukami and colleagues wrote.

**Inhibition of the endothelin pathway.** Endothelin antagonists like endothelin-1 (ET-1) have been shown to be elevated in kidneys of diabetic patients. ET antagonists may reduce growth factor expression and extracellular matrix (ECM) accumulation in rats. Bosentan has proved beneficial in studies, but it's not universally successful. Novel biphenylsulfonamide ET receptor antagonists are currently being investigated, but their role has not been adequately assessed, Dr. Fukami wrote.

**Inhibition of the vasopressin pathway.** Vasopressin (VP) antagonists have many actions relevant to the progression of renal disease. The first nonpeptide VP V1 antagonist OPC-21268 is being studied in patients with type 2 diabetes.

**Inhibition of neutral endopeptidase.** Vasodilator pathways also may offer a renoprotective mechanism. Neutral endopeptidase (NEP), a zinc-dependent metalloproteinase that promotes the degradation of vasodilatory hormones. Dr. Fukami wrote that a major target that is beginning to be developed is for agents that inhibit NEP and reduce vasoconstrictor hormones like Ang II and ET-1. The new class of drugs is known as VP inhibitors (VPis). "Our own group has shown that high-dose omapatrilat conferred superior renoprotective effects compared with an ACE inhibitor for the

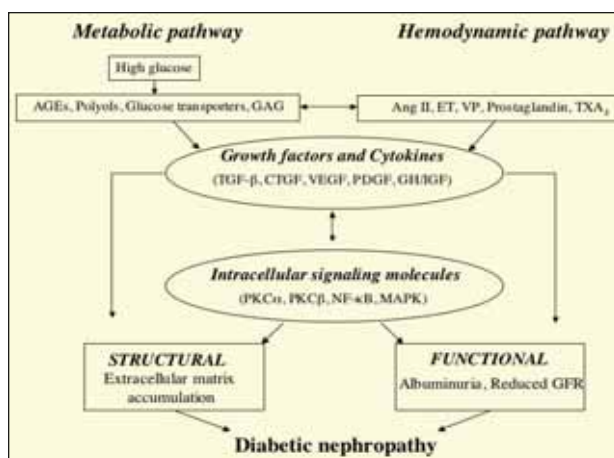


Figure 1. Schema outlining interactions among metabolic and hemodynamic factors, growth factors and cytokines, and intracellular signaling molecules in mediating diabetic nephropathy.

same reduction in blood pressure in a type 1 diabetic model of nephropathy. Other VPIs have been shown to be beneficial as well," Dr. Fukami wrote.

**Treatment with cyclooxygenase-2 inhibitors (COX 2), prostacyclin analogues and thromboxane A2 antagonist.** Studies have suggested that prostaglandins may be involved in the development of nephropathy. Experimental models suggest that, a highly selective COX-2 inhibitor may retard renal injury. The recent finding of a link to heart risk however, appears to render this treatment inappropriate.

Experimental studies have looked at a prostacyclin analogue, beraprost sodium, which reduced albuminuria in type 2 diabetic patients. Experimental studies have also demonstrated beneficial effects of thromboxane A2 (S-1452 and OKY-064).

**Inhibitions of growth factors and cytokines.** Inhibition of transforming growth factor beta may be useful in diabetic nephropathy. Although they are as yet not fully characterized as renoprotective agents, Dr. Fukami said. Connective tissue growth factor has been reported to act downstream in the development of diabetic complications. Preliminary reports have shown that blocking this activity might prevent the onset of diabetic nephropathy or reduce its severity. A phase 2 study of FG-3019 (FibroGen, Inc) is planned in patients with idiopathic pulmonary fibrosis. Vascular endothelial growth factor (VEGF) is a cytokine with a major role in the pathogenesis in diabetic retinopathy. It is, however, highly expressed in the kidney. Dr. Fukami wrote. Neutralizing VEGF antibodies may prove to be renoprotective. Platelet-derived growth factor (PDGF) has recently been shown to play a major role in cell proliferation and the

accumulation of ECM in the kidneys. Investigators have developed a PDGF receptor antagonist STI-571 (imatinib, Gleevec) that has been shown to be renoprotective in non-diabetic renal disease.

**Growth hormone/insulin-like growth factors.** "A large body of evidence now exists for various changes in the growth hormone/insulin-like growth factor (GH/IGF) pathway in the diabetic kidney," Dr. Fukami and colleagues wrote. Researchers are examining this pathway with octreotide, but with some hormonal side effects. Another derivative, PTR-3173 is being looked at, as well as a long-acting GH antagonist, G120K-PEG. The design of a 3-D model of the IGF-1 protein has allowed a series of selective antagonists to the IGF-1 receptor to be designed. All of this is experimental, and its treatment possibility is unknown.

**Inhibition of intracellular second messengers.** Protein kinase C (PKC) inhibitors have evolved over the last decade as increasing evidence has implicated PKC as an important mediator of diabetes-induced vascular dysfunction, Dr. Fukami said. Ruboxistaurin mesylate is a specific PKC-beta inhibitor (Eli Lilly and Company). A number of trials for various diabetic complications are in progress or have been completed. Other PKC isoform inhibitors include PKC-alpha. The nuclear factor kB inhibitor pyrrolidine dithiocarbamate has been studied and has shown to confer renoprotection. Mitogen-activated protein kinase inhibitors have been shown to have a role in nondiabetic disease. Findings from ongoing studies are being awaited to see if they may play a role in renal disease.

"Many of the experimental studies described provide novel insights into mechanisms responsible for diabetic nephropathy," Dr. Fukami and colleagues wrote. "The knowledge we have today on the pathogenesis of diabetic nephropathy indicates that diabetes-associated perturbation in various metabolic and hemodynamic pathways activate growth factors, cytokines and intracellular secondary messengers. At this state it is predicted that combination therapy with inhibitor of RAS and the advanced glycation pathway may be superior to either therapy along."

It is likely that recent insights into diabetic nephropathy will lead to a variety of new treatments with additional benefits not only in slowing, but also possibly reversing this progression of renal dysfunction in diabetes, they concluded. ■

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Fukami K, Cooper ME, Forbes JM. Agents in development for the treatment of diabetic nephropathy. *Expert Opin Investig Drugs*. 2005;14:279-294.