

REVIEW

Diabetic kidney disease: new treatment options



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Practice Points

- The current management of kidney disease in patients with diabetes focuses on achieving optimal glycemic control, blood pressure lowering and blockade of the renin–angiotensin system with ACE inhibitors or ARBs.
- While this is effective, its utility is partial at best, even in the setting of a supervised clinical trial, meaning that the majority of new cases of progressive kidney disease will not be prevented by best practice.
- A number of new agents have been developed to fill this clinical gap, including direct renin inhibitors, vitamin D analogs, phosphodiesterase inhibitors, heparanase inhibitors, thiamine, pyridoxamine, endothelin receptor inhibitors, xanthine oxidase inhibitors, antifibrotics, Nrf-2 agonists and urotensin II antagonists.
- There is insufficient evidence that any novel agents are able to achieve the degree of renoprotection needed by patients. At best, their effects are modest and some may be associated with an increased risk of off-target effects.
- The development of better-targeted ('smarter') drugs appears to be the best hope for renoprotective therapy in the future.

SUMMARY There is an urgent need for new approaches to protect the kidney and its functions in the increasing number of patients with diabetes. Although current strategies are effective, their effect is only partial and the majority of cases are not prevented, even by best practice. A number of new targets have been proposed, including direct renin inhibition, inhibition of fibrosis, activation of Nrf-2, sulodexide, endothelin I and urotensin II. However, the most advanced of these have all recently failed, while the remainder have demonstrated plausible efficacy only in small underpowered studies, and much research remains to both establish their efficacy and get them to the clinic. The development of better-targeted ('smarter') drugs appears to be the best hope for renoprotective therapy in the future.

At least half of all patients with diabetes presenting to their doctor will have chronic kidney disease (CKD), manifested by a reduction in estimated glomerular filtration rate (GFR) and/or increased urinary excretion of albumin (micro- or macro-albuminuria) [1]. In these patients, the development and progression of CKD is a major risk factor for morbidity and

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premature mortality. Indeed, excess mortality associated with diabetes is largely confined to those with CKD [2–4]. Consequently, preventing and managing diabetic kidney disease is now a key aim of diabetes management.

The current management of kidney disease in patients with diabetes focuses on achieving optimal glycemic control, blood pressure lowering and blockade of the renin–angiotensin system (RAS) with ACE inhibitors or ARBs. While this is effective, its utility is partial at best, even in the setting of a supervised clinical trial. For example, in the STENO-2 study, an intensive therapeutic program reduced new-onset macroalbuminuria by approximately half after 8 years of treatment [5]. Similarly, in the ADVANCE study, a combination of aggressive glucose lowering and blood pressure reduction with an ACE inhibitor reduced the incidence of new or worsening nephropathy by a third, and new-onset macroalbuminuria by just over a half [6]. This evidence should be an impetus for every practitioner and patient to further commit to current regimens. However, few patients with Type 2 diabetes are able to receive this kind of costly comprehensive therapy outside of clinical trials, meaning that the majority of new cases of progressive CKD will not be prevented by best practice. In this context, new paradigms for the prevention and management of kidney disease in patients with diabetes are urgently required.

This review aims to provide a summary of the new agents under investigation for managing kidney disease in patients with diabetes. This review has not considered the many new agents that may have indirect renoprotective benefits, such as the range of new drugs that improve glycemic, lipid or blood pressure control in diabetic individuals, and by doing so influence the progression of kidney disease in diabetes. Instead, a search of PUBMED, ClinicalTrials.gov and WHO International Clinical Trials Registry Platform has been performed for agents that have been or are being tested in Phase II/III clinical trials in patients with diabetes, in which renal outcomes (e.g., albumin excretion, GFR and change in creatinine) were predefined as primary or secondary outcomes. Initially the broad search terms ‘diabetes and kidney’, ‘nephropathy’, ‘diabetes’ and ‘albuminuria’ were used to identify studies, agents and strategies. Previous review articles on this subject captured through the initial search also served as a basis for identifying drugs that have been under evaluation.

Direct renin inhibition

Blockade achieved by ACE inhibitors and ARBs is only partial and short lived [7]. This is partly due to feedback induction of renin expression. As a result, renin inhibition has recently emerged as a means of reducing ‘escape’ from and amplifying the response to conventional RAS blockade. Positive effects on albuminuria have been reported in large clinical trials when the renin inhibitor aliskiren has been added to losartan [8] or irbesartan [9] in patients with diabetes and CKD. The combination of aliskiren with valsartan was also evaluated in patients with Type 2 diabetes in the ALTITUDE study [10]. However, this study was stopped in late 2011, as there was no prospect of demonstrating the treatment benefit, while at the same time there were safety concerns including risk of renal dysfunction, hyperkalemia, hypotension and strokes. The future development of this strategy is now on hold.

Vitamin D & its analogs

Vitamin D has an important role in the kidney and in kidney disease. Vitamin D deficiency is commonly observed in people with diabetes, especially those with CKD [11]. Treating vitamin D deficient patients with Type 2 diabetes with oral cholecalciferol to increase circulating vitamin D levels is able to reduce albuminuria and reduce urinary excretion of TGF- β , a profibrotic marker and mediator. However, the effects of cholecalciferol on calcium homeostasis potentially limit its utility in patients with diabetes, especially as those with CKD often exhibit aberrant vascular calcification. Selective vitamin D analogs that activate the vitamin D receptor, but cause little or no change in calcium/phosphate balance have, therefore, been recently studied. In the VITAL study, 281 patients with diabetes and CKD were randomized to receive a placebo, or 1 or 2 $\mu\text{g}/\text{day}$ of paricalcitol for 24 weeks [12]. Patients receiving the larger dose of 2 $\mu\text{g}/\text{day}$ showed a modest reduction in urinary albumin:creatinine ratio (20%; $p = 0.053$) and 24-h urinary albumin excretion (28%; $p = 0.009$) when compared with placebo [12], which was lost when paricalcitol was stopped. The lower dose had no significant effect. The results of these small short-term trials remain to be validated in longer and larger clinical trials.

Thiamine & its analogs

At least some of the damage induced by high glucose concentrations may be produced via

flux of metabolites through the glycolytic pathway, which leads to the formation of triose-phosphate intermediates and the generation of reactive α -oxoaldehydes, which are able to modify proteins to generate advanced glycation end products. Thiamine is a cofactor for transketolase, which reduces the formation of α -oxoaldehydes in response to excessive glycolytic flux by diverting triose phosphates down the pentose phosphate shunt [13]. At the same time, many patients with diabetes have relative or absolute deficiency of thiamine related to renal or tissue mishandling [14]. Although benfotiamine, a prodrug of thiamine monophosphate, failed to show any significant effect on albuminuria or markers of tubular injury in patients with Type 2 diabetes [15], in a small pilot trial, high-dose thiamine was able to reduce albumin excretion in patients with diabetes and CKD [16]. However, the potential utility of high-dose thiamine in patients with diabetes, particularly those with relative or absolute thiamine deficiency, remains to be tested in adequately powered studies.

Pyridoxamine

Pyridoxamine is a derivative of vitamin B₆. It is also thought to reduce advanced glycation end product accumulation, possibly by its ability to trap reactive carbonyl intermediates and reduce oxidative stress. Similar to thiamine, B6 vitamins may also be reduced in patients with diabetes, and especially those with renal disease or poor glucose control [17]. In initial Phase II clinical trials in patients with Type 1 and 2 diabetes, pyridoxamine appeared to slow the rise of serum creatinine during treatment [18]. However, a subsequent study in 312 patients with Type 2 diabetes and proteinuria reported no effect on renal function [19]. A positive effect was seen in a *post hoc* analysis of patients in the lowest tertile of baseline serum creatinine concentration (i.e., better renal function), while no effect was observed in the other two tertiles [19]. Another B₆ derivative with advanced glycation end product inhibitory activity, pyridoxal-5 phosphate, is also currently being studied in a clinical trial in patients with Type 2 diabetes [101]. However, a recent placebo-controlled trial of B vitamin therapy (B₆ and B₁₂ with folic acid) in 238 patients with Type 1 and 2 diabetes demonstrated an increase in stroke, cardiovascular events and all-cause mortality in the B vitamin group [20].

Inhibitors of fibrosis

Progressive fibrosis is a key mediator of functional loss in the diabetic kidney, and is viewed as a common downstream event triggered by a range of pathogenic mediators. Many of these processes converge on TGF- β . However, because of its pleiotropic effects, it is not suited to be a drug target. This has led investigators to look further downstream for potential targets that might be able to disrupt aberrant fibrogenesis, including CCN2 and PDGF.

CCN2 is required for the induction of new matrix synthesis through TGF- β . CCN2 levels are increased in patients with diabetes [21]. In one Phase I open-label study, a humanized neutralizing anti-CCN2 antibody (FG-3019) was studied in 24 subjects with diabetes and microalbuminuria [22,23]. Notably, urinary albumin excretion was reduced by approximately half ($p = 0.03$ versus baseline) [22]. However, as albuminuria is only a very indirect marker of its potential actions on fibrosis, larger trials examining renal fibrosis and harder outcomes, such as progression of renal function, are still required to confirm the potential of this strategy.

Pirfenidone is an antifibrotic drug used for the treatment of idiopathic pulmonary fibrosis. It works partly by inhibiting the expression of profibrogenic cytokines, including CTGF and PDGF. In a small, randomized, double-blind, placebo-controlled trial of 52 patients with diabetic kidney disease, low-dose (1200 mg) pirfenidone increased renal function compared with placebo, while the higher dose (2400 mg) had no effect, possibly due to the high drop-out rate [24]. There was no effect of either dose on albuminuria [24].

Tranilast (*N*-[3,4-dimethoxycinnamoyl]anthranilic acid) is an anti-inflammatory and antifibrotic compound originally developed for the treatment of hypertrophic scarring. It is used in Japan for the treatment of allergy, dermatitis and asthma. In small clinical studies, tranilast has been shown to modestly reduce albuminuria in patients with diabetes [25], and reduce the accumulation of renal collagen in patients with advanced nephropathy [26]. Again, none of these studies are large or long enough to confirm the utility of this approach.

Finally, the antibiotic doxycycline has also been evaluated for its antifibrotic effects, specifically its ability to inhibit matrix metalloproteinase. In one small, open-label, randomized study of 40 diabetic patients with proteinuria,

doxycycline was able to produce a modest reduction in protein excretion after 3 months of treatment, but this difference was no longer significant at 6 months [27]. The clinical utility of doxycycline is also potentially limited because of common side effects, including photosensitive rashes, catabolic effects and drug interactions.

Urotensin II receptor antagonism

Urotensin II is a small cyclic peptide that through its receptor triggers one of the most powerful vasoconstrictor responses known. Urotensin II also exerts a wide range of actions in other systems, including effects on cell growth and proliferation, sodium homeostasis and glomerular filtration. Urotensin II is also thought to be an important downstream effector for key pathogenic stimuli in the diabetic kidney, including RAS and TGF- β . A number of molecules have been developed as potential antagonists of urotensin II signaling. The most advanced is palosuran [28], which resulted in a modest reduction in urinary albumin when studied in 19 male patients with diabetic nephropathy exertion [29]. However, a subsequent larger study in 54 patients with diabetic kidney disease and hypertension demonstrated no significant effects on renal function or albuminuria after 4 weeks of treatment [30]. Neither study was sufficiently powered or long enough to confirm the presence or absence of renoprotective effects, and both studies used very low doses. More sensitive and selective urotensin receptor antagonists are also currently in development for other conditions [31], and these may be studied in diabetic kidney disease in the future.

Xanthine oxidase inhibitors

Inhibition of xanthine oxidase is widely used as a therapeutic strategy for the prevention and treatment of gout. As uric acid levels are also correlated with renal damage in diabetes, attention has recently turned to whether this strategy may also have direct renoprotective effects. In two small clinical studies, modest reductions in albuminuria following treatment with allopurinol have been reported [32,33]. However, dosing with allopurinol is complex, and serious side effects may be seen in some patients including hypersensitivity, aplasia, neuropathy and renal damage. The recent advent of the febuxostat, a nonpurine alternative to allopurinol for the management of gout, will be of great interest for patients with diabetes, not only because of

its comparative safety in patients with renal disease [34], but also because of its potential renoprotective effects through lowering uric acid levels. Febuxostat is currently recruiting for a specific clinical trial in diabetic CKD [102].

Nrf-2 agonists

The transcription factor Nrf-2 modulates cytoprotective responses affecting hundreds of genes involved in antioxidant, anti-inflammatory and detoxification pathways by binding to the *cis*-acting antioxidant response element found in the 5' flanking region of specific gene promoters. Coordinated augmentation of these defense signaling pathways via Nrf-2 activation has recently been investigated for the treatment of kidney disease in diabetes. In a randomized, double-blind, Phase IIb trial (BEAM), 227 Type 2 diabetic patients with advanced CKD (estimated GFR: 20–45 ml/min/1.73 m²) were randomized to receive 25, 75 or 150 mg of crystalline bardoxolone methyl once-daily for 52 weeks compared with placebo in a 1:1:1:1 design [35]. When compared with placebo, treatment with bardoxolone methyl (in addition to standard therapy) increased the estimated GFR by 5–10 ml/min. Significant increases were observed after as little as 4 weeks of treatment with bardoxolone methyl and this improvement in estimated GFR was sustained during one year of active treatment. The BEACON study was subsequently initiated in 2011 to test the utility of 20-mg SDD bardoxolone methyl once-daily orally in a randomized, double-blind, placebo-controlled, parallel-assignment Phase III trial in 1600 patients with CKD and Type 2 diabetes [103]. However, the safety monitoring board announced in late 2012 that the trial was being discontinued because of increased morbidity and mortality in participants receiving bardoxolone. The potential reasons for this unexpected finding remain to be disclosed.

Phosphodiesterase inhibitors

Phosphodiesterases (PDEs) are regulatory enzymes that breakdown the cyclic nucleotides cAMP and cGMP, which are key secondary messenger molecules in a number of pathways, including those triggered by nitric oxide, adrenaline and glucagon. By inhibiting the degradation of these nucleotides, PDE inhibitors prolong or enhance the signaling through these pathways. Several isoforms, including type 1, 2 and 5 PDE, are involved in the regulation of cyclical

nucleotides in vasculature and the kidney. Type 5 PDE selectively hydrolyze cGMP to potentiate nitric oxide dependent signaling. Type 5 PDE inhibitors such as sildenafil are widely used in the management of erectile dysfunction. Diabetic nephropathy is also associated with abnormalities of renal nitric oxide generation. Consequently, sildenafil may also have effects on the diabetic kidney [36]. In a single, small, randomized controlled trial (n = 40), sildenafil was shown to modestly reduce microalbuminuria in male diabetic patients, possibly by its actions to potentiate the renal effects of nitric oxide [37]. It is currently being more widely trialed specifically for its potential anti-albuminuric actions. Interestingly, dipyrindamole also inhibits type 5 PDE and can lower albuminuria in diabetic patients [38,39].

Pentoxifylline is a nonspecific PDE inhibitor used in the treatment of airways diseases. It has also been recently studied in patients with diabetes and CKD. In several small clinical studies in patients with diabetes, pentoxifylline has been shown to reduce albuminuria, over and above the actions of conventional RAS blockade [40,41]. A recent Cochrane meta-analysis from the available evidence suggested that pentoxifylline potentially offers some beneficial effects in renal function improvement and reduction in albuminuria and proteinuria. However, the current evidence remains insufficient to support its use in diabetic kidney disease. Larger trials are currently underway [42]. Cilostazol, a more selective inhibitor of type 3 PDE, is also currently being studied in patients with diabetes. Whether these agents are having direct effects on the kidney or indirect effects through action on platelets, enhanced lipolysis or other cAMP-dependent pathways, remains to be established.

Heparanase inhibitors

The endothelial glycocalyx forms a complex barrier that extends up to 0.5 μm from the endothelial surface to exclude macromolecules from the primary filtrate. The size and charge of this barrier are modified by diabetes, which is thought to contribute to the passage of albumin into the filtrate and subsequently into the urine [43]. The endothelial glycocalyx also plays a role in leukocyte–endothelial interactions and mechanotransduction that may be important for the progression of glomerular injury and inflammation [44]. Glycosaminoglycans are also an important constituent of the glomerular

basement membrane and its charge, particularly the highly sulfated glycosaminoglycan heparan. As a result, recent studies have attempted to use agents that directly modify glycosaminoglycan levels in the glomerulus as a means to influence the development and progression of diabetic kidney disease.

A number of investigators have studied the actions of low-molecular-weight heparins, heparinoids and heparitin sulfate as a means to restore the charge barrier and reduce albuminuria in patients with diabetes [45–47]. It is believed that these molecules act as competitive inhibitors of glomerular heparanase, thereby restoring heparan sulfate content and improving permselectivity to negatively charged macromolecules such as albumin. However, such approaches are limited because of the need for injection, anticoagulant actions and risk of bleeding, even in low doses. This led to the development of new formulations that are both orally bioavailable and had less effect on coagulation.

Sulodexide is a highly purified mixture of low-molecular-weight heparins (80%) and dermatan sulfate (20%), which concentrates in renal parenchyma after administration [48]. Initial small pilot studies suggested that sulodexide was effective in lowering albuminuria in diabetic patients with CKD [46,49–51]. However, this finding was not reproduced in two larger trials in 1056 patients with microalbuminuria (Sun-MICRO) [52] and 1248 patients with overt kidney disease (Sun-MACRO) [53]. In an accompanying editorial, it was concluded that “without the slightest indication of a favorable change in either albuminuria or serum creatinine level in the present trial, it seems likely that sulodexide as a treatment strategy for diabetic kidney disease will be relegated to the ash heap of history” [54]. Others have argued that the cheaper (Chinese) formulation used in the larger sulodexide trials was different from the initial (American) formulation in ways that alter its bioavailability and/or efficacy, meaning that the original findings may still be valid and worth further development [55].

Endothelin receptor antagonists

ET-1 is a vasoactive peptide that may affect the development of hypertension, angiogenesis, fibrosis, oxidative stress and inflammation associated with progressive kidney disease [56]. ET-1 levels are increased in patients with diabetes [57]. ET-1 is thought to contribute to the pathogenesis of CKD, predominantly through the binding and

Table 1. Key limitations for novel treatments used for the management of diabetic kidney disease.

Therapeutic strategy	Status	Ref.
Direct renin inhibitors	Uncertain following the negative efficacy and safety findings of the ALTITUDE trial	[10]
Vitamin D analogs	Borderline transient effects seen only with high doses and in one small study	[12]
Phosphodiesterase inhibitors	Small underpowered studies that still need to be confirmed	[37,40,41]
Heparanase inhibitors	Early data not reproduced in the larger Sun-MICRO and Sun-MACRO studies	[52,53]
High-dose thiamine	Small underpowered studies that still need to be confirmed	[16]
Benfotiamine	Experimental findings not reproduced in a larger trial with a renal end point	[15]
Pyridoxamine	Early <i>post hoc</i> results from pooled data not reproduced in the larger trial	[18,19]
Endothelin receptor inhibitors	Limited by safety concerns possibly due to activation of the ET _B receptor	[60]
Xanthine oxidase inhibitors	Currently the only positive findings are with allopurinol, whose broader utility is limited because of side effects	[32,33]
Antifibrotics	Small underpowered studies that still need to be confirmed	[22,24–27]
Nrf-2 agonists	Uncertain following the safety concerns raised by the BEACON trial	[103]
Urotensin II antagonists	Small underpowered studies that need to be confirmed	[28,29]

activation of the endothelin receptors, chiefly the ET_A receptor. Consequently, recent clinical studies have explored the potential utility of blocking this receptor. The first agent to be studied was atrasentan, which reduced proteinuria in a small 12-week trial in ten patients with Type 1 diabetes [58]. This was confirmed in a small dose-finding study in 89 patients with diabetic nephropathy already receiving RAS inhibitors [59]. More recently, the ASCEND trial studied 1392 participants with Type 2 diabetes treated with avosentan (25 or 50 mg) or placebo for 3 and 6 months. Treatment with avosentan was able to reduce the urinary albumin:creatinine ratio, particularly when treatment was given in addition to ACE inhibition [60,61]. However, this was at the cost of fluid overload, congestive heart failure and an excess of cardiovascular events, which led to the early termination of this trial [60]. It has been suggested that fluid retention may be attributable to nonspecific blockade of ET_B receptors in the kidney [62], leaving the future development of more selective high-affinity ET_A receptor blockers for the management of diabetic kidney disease a possibility.

Conclusion & future perspective

There is an urgent need for renoprotective therapies to manage the increasing numbers of patients with diabetes and their burden of renal complications. Current treatments are only partly effective and only have indirect actions on the kidney. Moreover, while there is a significant treatment gap, there are, at present, no new drugs that could fill this in the near future (Table 1). All of the most advanced clinical development programs over the last decade have failed, including

direct renin inhibitors, endothelin antagonists and, most recently, bardoxolone methyl. The remaining agents have demonstrated plausible efficacy only in small underpowered studies and much remains to get them to the clinic. Indeed, when tested in larger longer studies, some of their putative renoprotective actions have not been reproducible, such as those of sulodexide, palosuran, benfotiamine and pyridoxamine. Sadly, when taken together, such failures will serve to stifle the development of new agents at precisely the time that such agents are required.

However, the future is not entirely bleak. The advent of new techniques to facilitate the structure-based design of highly selective drugs offers enormous promise. Ever-expanding computing power combined with detailed molecular modeling and *in silico* screening make it possible to put drugs exactly in the right place, while minimizing off-target actions and side effects. It is likely that the future management of kidney disease in diabetes will be driven by these smarter (better-targeted) drugs. The trick now is to find the best target.

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