Targeting Inflammation in Diabetic Kidney Disease: Is There a Role for Pentoxifylline?

David J. Leehey

Abstract

Diabetic kidney disease (DKD) is the most common cause of ESKD in the United States and worldwide. Current treatment for DKD includes strict glycemic control and normalization of BP with renin-angiotensin-aldosterone system (RAAS) blockade. Although RAAS blockers slow progression of disease, they do not generally prevent ESKD and none of the studies with these agents in DKD included patients who were nonproteinuric, which make up an increasingly large percentage of patients with diabetes now seen in clinical practice. Recent studies with glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 (SGLT2) inhibitors have shown beneficial renal effects, and the benefits of SGLT2 inhibitors likely extend to patients who are nonproteinuric. However, there remains a need to develop new therapies for DKD, particularly in those patients with advanced disease. A role of chronic low-grade inflammation in microvascular complications in patients with diabetes has now been widely accepted. Large clinical trials are being carried out with experimental agents such as bardoxolone and selonsertib that target inflammation and oxidative stress. The Food and Drug Administration–approved, nonspecific phosphodiesterase inhibitor pentoxifylline (PTX) has been shown to have anti-inflammatory effects in both animal and human studies by inhibiting the production of proinflammatory cytokines. Small randomized clinical trials and meta-analyses indicate that PTX may have therapeutic benefits in DKD, raising the possibility that a clinically available drug may be able to be repurposed to treat this disease. A large, multicenter, randomized clinical trial to determine whether this agent can decrease time to ESKD or death is currently being conducted, but results will not be available for several years. At this time, the combination of RAAS blockade plus SGLT2 inhibition is considered standard of care for DKD, but it may be reasonable for clinicians to consider addition of PTX in patients whose disease continues to progress despite optimization of current standard-of-care therapies.

Introduction

Diabetic kidney disease (DKD) is the most common cause of ESKD in the United States (1). The pathogenesis of DKD includes mesangial expansion, endothelial dysfunction, loss of glomerular podocytes, and interstitial fibrosis. The classic natural history of DKD is the development of albuminuria, with small amounts of albuminuria (microalbuminuria) progressing to overt albuminuria (macroalbuminuria) and nephrotic syndrome, eventually leading to ESKD. The characteristic renal pathologic findings are diffuse and nodular glomerulosclerosis (2). Proteinuria is an important predictor of outcome in CKD, including DKD (3,4). Risk factors for progression to ESKD include hyperglycemia, hypertension, severity of albuminuria, and presence of retinopathy (5). High salt intake and arteriosclerosis are implicated in the development of DKD, especially in patients with type 2 diabetes mellitus (DM) (6). Patients with DKD are at markedly increased risk for cardiovascular events and mortality (7,8).

Current treatment for DKD includes strict glycemic control and normalization of BP, with renin-angiotensin-aldosterone system (RAAS) blockade being the cornerstone of antihypertensive therapy (9). Although RAAS blockers such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are effective in slowing progression of disease, they do not generally prevent progression to ESKD (10,11). Combination RAAS blockade has not been proven to be more effective than monotherapy and is associated with increased adverse events (12). Recent studies with glucagon-like peptide-1 receptor agonists and, in particular, sodium-glucose cotransporter-2 (SGLT2) inhibitors have shown beneficial renal effects (13,14). In the CREDENCE study, the first study since those with RAAS blockers to show a reduction in hard renal end points, there was an impressive 34% reduction in ESKD and also a reduction in cardiovascular mortality with the SGLT2 inhibitor canagliflozin (14).

Albuminuric versus Nonalbuminuric DKD

In recent years, possibly due to better treatment of diabetes and hypertension and the use of RAAS blockers, the prevalence of nonalbuminuric versus albuminuric DKD has increased, especially in type 2 DM. In a cross-sectional analysis of United States adults with diabetes from the National Health and Nutrition Examination Survey (NHANES) III (1988–1994), 35% of subjects with an eGFR of <60 ml/min per 1.73 m^2 were normoalbuminuric, and albuminuria and retinopathy were both absent in 30% of subjects with reduced eGFR (15). In subsequent cross-sectional analyses of NHANES

Veterans Affairs Hospital, Hines, Illinois; and Loyola University Medical Center, Maywood, Illinois

Correspondence: Dr. David J. Leehey, Hines Veterans Affairs Hospital, 111L, Hines, IL 60141. Email: david.leehey@va.gov

data, higher adjusted prevalence rates (approximately 50%) for the nonalbuminuric phenotype among individuals with reduced eGFR were observed (8). Similar findings have been observed in cohorts of patients with type 2 DM outside the United States and in those enrolled in multicenter, multinational, interventional studies (16).

Currently there are no large trials that have been performed in nonalbuminuric DKD. It is not known whether RAAS blockers have similar benefits in these patients. Concern has been raised that RAAS blockers, by preventing constriction of the efferent arteriole, may actually increase susceptibility to AKI in patients who are nonalbuminuric (16). With respect to SGLT2 inhibitors, in a *post hoc* analysis of data from the CANVAS program, canagliflozin slowed the annual loss of kidney function across albuminuria subgroups, suggesting that SGLT2 inhibitors may also be beneficial in patients who are nonalbuminuric, although there was a greater absolute benefit in participants with severely increased albuminuria (17). The concern about AKI that can occur with RAAS blockers does not appear to extend to SGLT2 inhibitors (18). The beneficial effect of SGLT2 inhibitors might attenuate with declining kidney function and there is currently no clear evidence for benefit in those with eGFR of <30 ml/min per 1.73 m^2, although such studies are being conducted (19). The increasing prevalence of nonalbuminuric or minimally albuminuric DKD underscores the need to develop new therapies for nonalbuminuric DKD, particularly in those patients with advanced CKD.

Nonalbuminuric DKD is thought to be predominantly due to vascular and tubulointerstitial lesions, and decline in renal function in such patients may be at least partly due to ongoing inflammation not entirely remediated by current therapies (16). Therefore, there is much interest in the development of anti-inflammatory agents for the treatment of DKD.

Inflammation in DKD

DKD has traditionally been considered to be caused by the adverse effects of hyperglycemia (metabolic theory) and hemodynamic alterations that increase systemic and intraglomerular pressure (hemodynamic theory) in patients who are genetically predisposed. Nearly three decades ago, Hasegawa et al. (20) initially suggested, based on studies in diabetic animals, that proinflammatory cytokines might be involved in the pathogenesis of DKD. The source of cytokine production by the kidneys in DM is from both infiltrating macrophages and resident kidney cells. Production of reactive oxygen species, proinflammatory factors, and certain growth factors (such as TGF-β) can induce renal damage, and macrophage-depletion studies in rodent models have shown a causal role for macrophages in the progression of DKD (21). In a human biopsy study, Nguyen et al. (22) reported that accumulation of macrophages was more prevalent in the interstitium than in the glomeruli and that interstitial macrophages correlated strongly with proteinuria, decline in renal function, and extent of interstitial fibrosis. Various types of renal cells (endothelial, mesangial, epithelial, and tubular cells) are capable of synthesizing proinflammatory cytokines such as TNF-α, IL-1, and IL-6. These cytokines, acting in a paracrine or autocrine manner, contribute to the pathophysiology of DKD (23). Plasma concentrations of proinflammatory cytokines are elevated in patients with type

2 DM (24,25) and increase as nephropathy progresses (26,27). Inflammation and oxidative stress are associated with both micro- and macrovascular diabetic complications (28,29).

TNF-α is an important proinflammatory cytokine and has been much studied in DKD. In a study by Navarro et al. in patients with type 2 DM with mild proteinuria (<1 g/d), serum concentrations of high-sensitivity C-reactive protein and serum and urine concentrations of TNF-α correlated with albuminuria. Urinary TNF-α levels increased significantly as nephropathy progressed (30). In a recent meta-analysis, serum and urinary concentrations of TNF-α are elevated in patients with DKD and these concentrations increase concomitantly with the progression of CKD (31). This cytokine is cytotoxic to glomerular cells *in vitro* (32) and increases protein permeability in isolated glomeruli, independent of hemodynamic alterations or effects of recruited inflammatory cells (33). In diabetic animals, increased urinary as well as renal interstitial concentrations of TNF-α precede the rise in albuminuria (34). In a proof-of-concept study, Moriwaki et al. (35) found that diabetic rats treated with the chimeric anti–TNF-α antibody infliximab showed a reduction in albuminuria.

Proinflammatory ILs are also involved in the pathogenesis of DKD. In a biopsy study, IL-6 mRNA was expressed by glomerular resident cells and interstitial cells in patients with DKD (36). Most cells in the area of mesangial proliferation were strongly stained for IL-6 mRNA, and some positive cells were found in the Kimmelstiel–Wilson nodular lesions. In the interstitium, some tubules and infiltrating cells were also positively stained for IL-6 mRNA, and the interstitial expression of IL-6 mRNA correlated significantly with the degree of interstitial injury. In another biopsy study in type 2 DM, glomerular basement membrane width was directly correlated with IL-6 (37), and both IL-1 and IL-6 have been shown to be overproduced by interstitial and glomerular cells in diabetes (37–39). In streptozotocin diabetes in the rat, renal cortical mRNA expression for TNF-α, IL-1, and IL-6 was 2.4-, 1.2-, and 3.4-fold higher than in nondiabetic rats. Albuminuria was significantly associated with renal mRNA expression of TNF-α and IL-6 but not IL-1 (38). Another proinflammatory IL, IL-18, may also play an important role in DKD (40). Chronically increased levels of inflammation are associated with an increase in C-reactive protein, the latter of which is associated with many pathologic conditions in diabetes, including atherosclerosis and DKD (41).

Targeting Inflammation in DKD

A role of chronic low-grade inflammation in the microvascular complications in patients with diabetes has now been widely accepted (42,43). Several approaches have been proposed to treat inflammation in DKD, including lifestyle modifications (diet and exercise) and medications. Anti-inflammatory effects may explain some of the benefits of SGLT2 inhibitors and possibly also glucagon-like peptide-1 receptor agonists (21). In addition, three large randomized controlled trials specifically targeting inflammation in DKD have been or are currently being performed.

Bardoxolone

Bardoxolone targets oxidative stress and reduces inflammation by inhibiting proinflammatory cytokines and

decreasing TGF-β and extracellular matrix proteins (44). The BEACON study using the NF erythroid 2-related factor 2 activator bardoxolone methyl was stopped prematurely due to an increase in adverse cardiovascular outcomes, and thus its role in ESKD prevention could not be assessed (45). However, in a subsequent *post hoc* analysis, patients treated with bardoxolone were significantly less likely to experience the composite renal end point (46). Bardoxolone is being studied again in Japan in a Phase 3 Study of Bardoxolone Methyl in Patients with DKD; AYAME Study (NCT03550443), with an estimated completion date of March 2022. Patients with an eGFR of 15–60 ml/min per 1.73 m² will be studied. The primary outcome is time to onset of a ≥30% decrease in eGFR from baseline or ESKD.

Selonsertib

Glucose can activate the transcription factor NF-κB, resulting in increased inflammatory gene expression, in part through oxidative stress, advanced glycation end products (AGEs), protein kinase C, and mitogen-activated protein kinases. Apoptosis signal–regulating kinase 1 (ASK1) acts as an upstream regulator for the activation of p38 mitogen-activated protein kinases and c-Jun N-terminal kinase. Oxidative stress increases ASK1 activity, promoting inflammation, apoptosis, and fibrosis. In animal models of DKD, ASK1 inhibition reduces progressive kidney injury, inflammation, and fibrosis (47). Selonsertib is a highly selective, potent, small-molecule inhibitor of ASK1 being developed as a once-daily oral agent for the management of DKD. In a recent double-blind, placebo-controlled, phase 2 trial, selonsertib appeared safe with no dose-dependent adverse effects over 48 weeks. Effects on urinary albumin-to-creatinine ratio (UACR) did not differ between selonsertib and placebo, but exploratory *post hoc* analyses suggest that selonsertib may slow DKD progression (48). A phase 3 trial, Efficacy and Safety of Selonsertib in Participants with Moderate to Advanced DKD (MOSAIC; NCT04026165) is currently enrolling patients with type 2 DM and eGFR of 20–60 ml/min per 1.73 m² with albuminuria and is estimated to be completed in December 2024. Clinical outcome measures are time to ≥40% decline in eGFR from baseline, ESKD, or death due to kidney disease.

Pentoxifylline

Phosphodiesterases (PDEs) are a class of enzymes that hydrolyze cAMP and cyclic guanosine monophosphate and are involved in many physiologic processes including cell proliferation and differentiation, cell-cycle regulation, gene expression, cellular metabolism, apoptosis, and inflammation. PDEs are composed of 11 different families and each family contains different subtypes. Pentoxifylline (PTX) is a methylxanthine derivative with pleomorphic effects including nonspecific inhibition of PDEs. PTX was approved by the US Food and Drug Administration for the treatment of intermittent claudication >30 years ago (49). Clinical experience has indicated that this agent has a favorable safety profile; therefore, if it can be shown to be efficacious, it could be an attractive agent to treat DKD (50).

PTX: Mechanism of Action. PTX is known as a hemorheologic agent because it results in a reduction in blood viscosity, erythrocyte aggregation, erythrocyte rigidity, and platelet aggregation. The increase in red blood cell flexibility and deformability leads to improved blood flow (51). In addition, PTX has been shown to have immunomodulatory and anti-inflammatory effects (52). PDE inactivates the intracellular second messengers cAMP and cyclic guanosine monophosphate. PTX predominantly inhibits the PDE3 and PDE4 isoforms and thus primarily affects cAMP. The PTX-induced increase in cAMP will in turn increase protein kinase A activation, leading to a reduction in synthesis of the inflammatory cytokines IL-1, IL-6, and TNF-α (43,50).

PTX: Basic and Translational Studies. PTX has an inhibitory effect on primary human renal fibroblasts in a time- and dose-dependent fashion (53). In animal studies in both diabetic and nondiabetic models, PTX exhibited a marked antiproteinuric effect while attenuating interstitial inflammation and progression of renal injury (34,38,54–57). In the streptozotocin-diabetic rat, PTX treatment can lead to improvement in signs of inflammation, oxidative stress, and subsequent fibrosis by acting on cytokine signaling (28,58). Similarly, in an alloxan-induced diabetic rat model, PTX also exerted anti-inflammatory effects *via* decreasing the levels of TNF-α and IL-6 (59). PTX may also be able to decrease inflammation generated by formation of AGEs. AGEs cause a series of signaling cascade events that result in an increase in oxidative stress and production of proinflammatory cytokines (*i.e.*, IL-6, IL-1, and TNF-α) (60). PTX has been shown to decrease oxidative stress in diabetic animal models (58).

Another possible anti-inflammatory effect of PTX may be stimulation of Klotho, a type I single-pass transmembrane protein predominantly expressed in the kidneys (61). Reduced renal Klotho expression has been observed in biopsies from patients with early stages of DKD (62), and decreased plasma soluble Klotho may be an early biomarker for predicting DKD progression in patients with type 2 DM (63). The proinflammatory cytokines TNF-α and TNF-like weak inducer of apoptosis decrease renal Klotho expression mediated by NF-κB (64–66). In a recent *post hoc* analysis of the PREDIAN trial by Navarro-González *et al.* (67), administration of PTX to patients with type 2 DM with CKD stages 3 and 4 resulted in some reduction of serum and urinary TNF-α and increased serum and urinary Klotho concentrations. The mechanisms by which PTX is thought to inhibit inflammation are depicted in Figure 1.

PTX: Clinical Trials. Clinical data supporting a role for PTX in DKD have been accumulating for the past two decades. Most of these trials have used a small number of subjects and were of short duration, and all used surrogate end points such as reduction in proteinuria and changes in eGFR and not hard end points such as ESKD and death (Table 1) (68–82). Some, but not all, of these studies were placebo controlled, and none used intention-to-treat analysis or reported blinding of data assessors. Only the PREDIAN trial (73) provided details about the process of allocation concealment. In this study, the renoprotective effects of 2 years of PTX therapy in addition to RAAS blockade was evaluated in 169 white patients with type 2 DM and stage 3 or 4 CKD and urinary albumin excretion of >30 mg/24 h. Treatment with PTX (1200 mg/d) decreased proteinuria and urinary concentration of TNF-α and slowed decline in eGFR. At study end, eGFR had decreased by
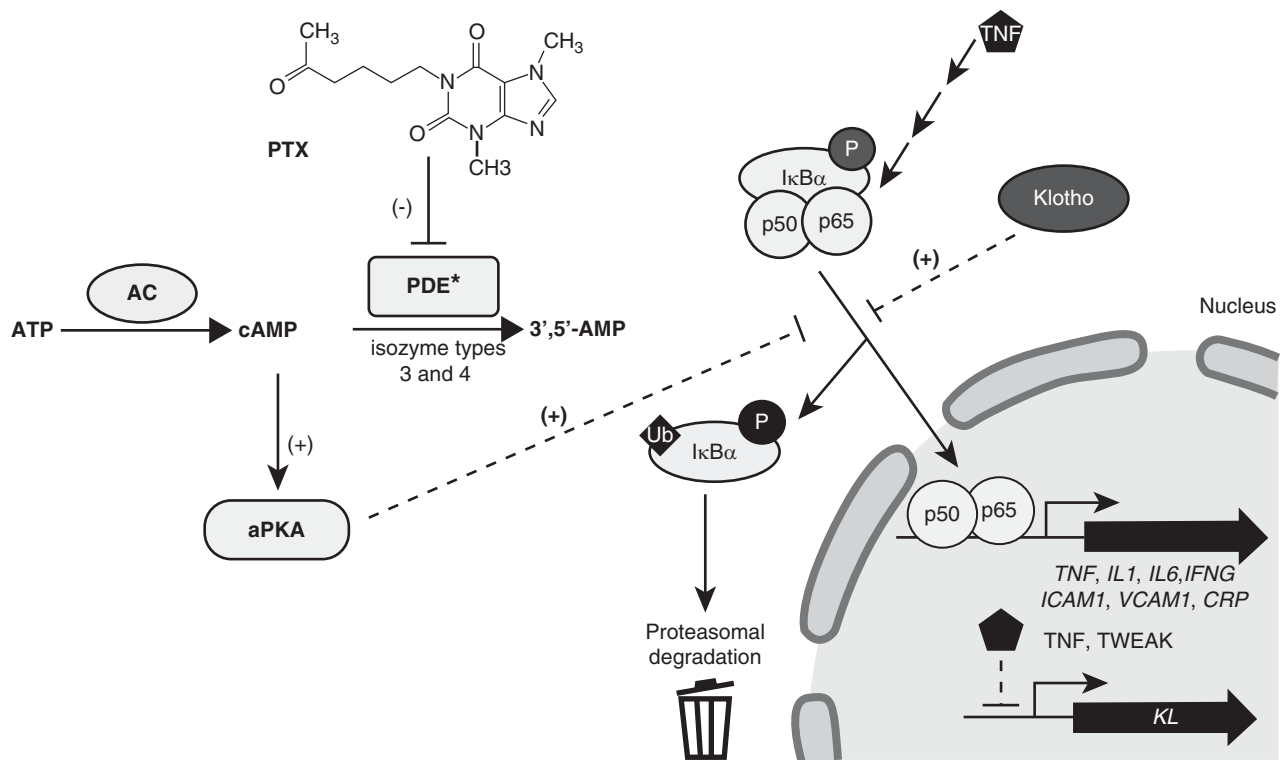
Figure 1. | **Pentoxifylline inhibits phosphodiesterase activity, increasing cAMP levels that activate protein kinase A.** Active protein kinase A (aPKA) would inhibit ubiquitination that drives inhibitor of κ B α (IκBα) to 26S proteasome degradation and p50/p65 activation of the expression of cytokines and other genes. Decreased levels of TNF-α (TNF) and TNF-related weak inducer of apoptosis (TWEAK) increases Klotho (KL) expression, whereas KL inhibits the production of proinflammatory cytokines and TNF-induced adhesion molecules. AC, adenylate cyclase; CRP, C-reactive protein; ICAM1, intercellular adhesion molecule 1; IFNG, IFN-γ; P, phosphorylation; p50, NF-κB p50 subunit (NF-κ-light-chain-enhancer of activated B cells 1); p65, NF-κB p65 subunit (RelA; v-rel avian reticuloendotheliosis viral oncogene homolog A); PTX, pentoxifylline; VCAM1, vascular cell adhesion molecule 1. Reprinted from reference 43 (Donate-Correa J, Tagua VG, Ferri C, Martín-Núñz E, Hernández- Carballo C, Ureña-Torres P, Ruiz-Ortega M, Ortiz A, Mora-Fernández C, Navarro-González JF: Pentoxifylline for renal protection in diabetic kidney disease. A model of old drugs for new horizons. J Clin Med 8: E287, 2019), which is available under the terms of the Creative Commons Attribution License.

2.1 ml/min per 1.73 m^2 in the PTX group versus 6.5 ml/min per 1.73 m^2 (between-group difference of 4.3 ml/min per 1.73 m^2, $P=0.001$). The difference in reduction of eGFR was evident at 6 months and reached statistical significance at 1 year. There were no serious adverse events, and the only adverse events that occurred more commonly than with placebo were digestive symptoms (abdominal discomfort, flatus, dyspepsia, nausea, and vomiting), which were about twice as common in the treated group. Only one patient needed to have PTX withdrawn because of side effects. The favorable safety profile is supported by clinical experience in using this agent in treatment of peripheral vascular disease for decades with minimal side effects. Although these results are very intriguing, there are some limitations to the PREDIAN trial. First, the study enrolled only white patients. Second, it was a single-center study, which may limit its generalizability. Third, the study was open label and not placebo controlled. Finally, and most importantly, the study was not powered to detect differences in hard outcomes such as ESKD and mortality.

The Veterans Affairs Cooperative study Pentoxifylline in DKD (PTXRx; NCT03625648) is comparing PTX to placebo in patients with type 2 DM and eGFR of 15–60 ml/min per 1.73 m^2, targeting high-risk patients according to the "heat map" of the Kidney Disease Improving Global Outcomes (83). Patients will need to have an eGFR of 15 to <30 ml/min per 1.73 m^2, or an eGFR of 30 to <45 ml/min per 1.73 m^2 with UACR >30 mg/g, or eGFR 45 to <60 ml/min per 1.73 m^2 with UACR >300 mg/g. The primary outcome is time to ESKD or all-cause mortality. The study plans to randomize 2510 patients, began enrolling in November 2019, and is predicted to be completed by 2030.

PTX: Meta-Analyses. An early meta-analysis published in 2008 suggested that decreased production of proinflammatory cytokines was the most likely explanation for the antiproteinuric action of PTX in patients with DKD (84). In a Cochrane meta-analysis of the renoprotective effect of PTX when used in combination with RAAS inhibitors (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers) published in 2012 (85), PTX reduced albuminuria and proteinuria, with no obvious serious adverse effects in patients with DKD. However, most included studies were poorly reported, small, and methodologically flawed. Since the Cochrane analysis there have been several other meta-analyses published. Tian *et al.* (86) reported eight studies with a total of 587 patients (all

Table 1. Renal effects of pentoxifylline in clinical trials

Study	Duration	Entry Criteria	Groups	N	Intervention	Placebo Controlled	Outcome
Aminorroaya et al. (68)	2 mo	Type 2 DM; UPE >300 mg/24 h	PTX versus captopril	39	PTX 1200 mg/d	No	Decrease in UPE in both groups (PTX, 29% reduction, $P<0.05$; captopril, 38% reduction, $P<0.01$)
Ghorbani et al. (69)	6 mo	Type 2 DM; persistent UPE >150 mg/24 h despite RAAS blockers	PTX+losartan and enalapril versus losartan and enalapril	100	PTX 400 mg/d	No	Decrease in UPE (PTX, 69% reduction, $P<0.001$; control, 16% reduction, $P=NS$); increase in creatinine clearance (PTX, 6% increase; control, 0.7% decrease, $P=0.04$)
Guerrero-Romero et al. (70)	4 mo	Type 1 and type 2 DM with overt proteinuria	PTX versus placebo	86	PTX 1200 mg/d	Yes	Decrease in UPE (type 1: PTX, 86% reduction, $P<0.01$; placebo, 7% reduction, $P=NS$; type 2: PTX, 93% reduction, $P<0.001$; placebo, 6% increase, $P=NS$)
Han et al. (71)	6 mo	Type 2 DM; UACR >30 mg/g	PTX versus placebo	174	PTX 1200 mg/d	Yes	Decrease in UACR (PTX, 23% reduction; placebo, 4% reduction; $P=0.012$)
Harmankaya et al. (72)	9 mo	Type 2 DM; persistent microalbuminuria	PTX+lisinopril versus lisinopril	50	PTX 600 mg/d	No	Decrease in UAE (PTX, 42% reduction, $P<0.05$; control, 35% reduction, $P<0.05$)
Navarro-González et al. (73)	24 mo	Type 2 DM; stage 3–4 CKD; UAE >30 mg/24 h	PTX and ACEi or ARB versus ACEi or ARB	169	PTX 1200 mg/d	No	Decrease in UAE (PTX, 15% reduction; control, 6% increase; $P=0.001$); decrease in eGFR decline (PTX, 2.1 ml/min per 1.73 m^2; control, 6.5 ml/min per 1.73/m^2; $P<0.001$)
Navarro et al. (74)	6 mo	DM (type not stated) with creatinine clearance <35 ml/min	PTX versus standard Rx	24	PTX 400 mg/d	No	Decrease in UPE (PTX, 59% reduction, $P<0.05$; control, $P=NS$)
Navarro et al. (75)	4 mo	Type 2 DM with proteinuria (<3 g/d)	PTX and ACEi or ARB versus ACEi or ARB	45	PTX 1200 mg/d	No	Decrease in UPE (PTX, 15% reduction, $P<0.001$; control, 0.5% reduction, $P=NS$)
Navarro et al. (76)	4 mo	Type 2 DM; UAE >300 mg/24 h, normal renal function	PTX and ARB versus ARB	61	PTX 1200 mg/d	No	Decrease in UAE (PTX, 17% reduction; control, 6% reduction, $P<0.001$)
Oliaei et al. (77)	3 mo	Type 2 DM; proteinuria >500 mg/d	PTX+ACEi or ARB versus ACEi or ARB	56	PTX 1200 mg/d	Yes	Decrease in proteinuria (PTX, 61% reduction; placebo, 20% reduction, $P<0.001$)
Rodríguez-Morán et al. (78)	6 mo	Type 2 DM; UAE 20–200 mcg/min; no RAAS blockers	PTX versus captopril	130	PTX 1200 mg/d	No	Equivalent decrease in UAE (PTX, 77% reduction; captopril, 76% reduction; $P=NS$)
Rodriguez-Morán et al. (79)	16 wk	Type 2 DM; UAE 200–200 mcg/min; no RAAS blockers	PTX versus placebo	40	PTX 1200 mg/d	Yes	Decreased UAE (PTX, 74% reduction, $P=0.02$; placebo, 7% reduction, $P=NS$)
Roozbeh et al. (80)	6 mo	Type 2 DM; UPE >500 mg/d	PTX+captopril versus captopril	70	PTX 1200 mg/d	No	Decrease in UPE (PTX, 56% reduction; placebo, 28% reduction; $P=0.007$)
Shahidi et al. (81)	6 mo	Type 2 DM with microalbuminuria; eGFR >60 ml/min per 1.73 m^2	PTX versus placebo	40	PTX 1200 mg/d	Yes	No difference in UACR, BP, or eGFR (PTX, 2% reduction in UACR; placebo, 1% increase in UACR; $P=NS$)
Solerte et al. (82)	12 mo	Type 1 DM; UPE >500 mg/d	PTX versus conventional Rx	21	PTX 1200 mg/d	No	Decrease in UPE (PTX, 47% reduction, $P<0.01$; conventional, 42% reduction, $P<0.01$); increase in creatinine clearance (PTX, 20% increase, $P<0.01$; conventional, 14% increase, $P<0.01$)

DM, diabetes mellitus; UPE, urine protein excretion; PTX, pentoxifylline; RAAS, renin-angiotensin-aldosterone system; UACR, urinary albumin-to-creatinine ratio; UAE, urine albumin excretion; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; Rx, prescription.

diabetic), in which PTX was combined with RAAS blockers. Addition of PTX resulted in further reductions in albuminuria, proteinuria, and urinary TNF-α, but did not result in significant changes in glycated hemoglobin (hemoglobin A_{1c}), serum creatinine, creatinine clearance, systolic BP, or diastolic BP. Jiang *et al.* (87) reported 12 trials with 613 participants (most included only patients with diabetes). PTX significantly decreased proteinuria compared with the placebo or no-treatment groups and led to a lesser decline of eGFR. There were no significant differences in BP or adverse events. Most of the included studies were small and of short duration, with the exception of the PREDIAN trial. Meta-analyses by Leporini *et al.* (88) and Liu *et al.* (89) also concluded that there is evidence for some renoprotective effects of PTX but no conclusive data proving the usefulness of this agent for improving renal outcomes in CKD. Moreover, meta-analyses of small trials are insufficient to guide therapy because they tend to overestimate treatment effects compared to large trials, partly due to publication bias.

Conclusions

Although there is much evidence that inflammation is important in the progression of DKD, there are no large clinical trials showing benefit of anti-inflammatory therapies. The current literature suggests that PTX may have therapeutic benefits in addition to RAAS blockade in DKD. PTX could be beneficial in patients unable to tolerate RAAS blockade or in those with very advanced CKD in whom RAAS blockade may carry increased risk. The available evidence thus suggests the possibility of the use of PTX as a valuable repurposing of an old drug in the treatment of DKD. However, a large-scale, multicenter, randomized clinical trial is needed to determine whether this agent can reduce hard end points such as ESKD and death. Such a trial is currently being conducted (PTXRx; www.clinicaltrials.gov, NCT03625648), but the results will not be available for several years. At this time, the combination of RAAS blockade plus SGLT2 inhibition is considered standard of care for patients with type 2 DM and CKD (eGFR 30 to $\leq$60 ml/min per 1.73 m^2 or UACR >30 mg/g, particularly >300 mg/g) to prevent progression of CKD and adverse cardiovascular outcomes (90). It may be reasonable for clinicians to consider addition of PTX in patients with type 2 DM whose CKD continues to progress despite optimization of current standard-of-care therapies.

Author Contributions

D. Leehey wrote the original draft of the manuscript, reviewed and edited the manuscript, and was responsible for conceptualization, project administration, resources, and software.

Disclosures

D. Leehey has nothing to disclose.

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