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

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Abstract

Diabetic kidney disease (DKD) is the most common cause of end-stage renal disease (ESRD) in the U.S. and worldwide. Current treatment for DKD includes strict glycemic control and normalization of blood pressure with renin-angiotensin-aldosterone system (RAAS) blockade. Although RAAS blockers slow progression of disease they do not generally prevent ESRD, and none of the studies with these agents in DKD included non-proteinuric patients, which make up an increasingly large percentage of diabetic patients now seen in clinical practice. Recent studies with glucagon-like peptide-1 receptor agonists and sodium-glucose co-transport-2 (SGLT2) inhibitors have shown beneficial renal effects, and the benefits of SGLT2 inhibitors likely extend to non-proteinuric patients. 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 the microvascular complications in diabetic patients 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 FDA-approved non-specific 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 ESRD or death is currently being conducted, but results will not be available for several years. At the current 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 end-stage renal disease (ESRD) in the U.S. [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 ESRD. The characteristic renal pathologic findings are diffuse and nodular glomerulosclerosis [2]. Proteinuria is an important predictor of outcome in chronic kidney disease (CKD), including DKD [3,4]. Risk factors for progression to ESRD 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 type 2 diabetes mellitus (DM) patients [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 blood pressure (BP), with renin-angiotensin-aldosterone system (RAAS) blockade the cornerstone of anti-hypertensive therapy [9]. Although RAAS blockers such as angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are effective in slowing progression of disease, they do not generally prevent progression to ESRD [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 co-transport-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 endpoints, there was an impressive 34% reduction in ESRD and also a reduction in cardiovascular mortality with the SGLT2 inhibitor canagliflozin [14].
**Albuminuric vs. Non-albuminuric DKD**

In recent years, possibly due to better treatment of diabetes and hypertension and the use of RAAS blockers, the prevalence of non-albuminuric vs. albuminuric DKD has increased, especially in type 2 DM. In a cross-sectional analysis of U.S. adults with diabetes from the NHANES 1988–1994, 35.1% of subjects with an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m were normoalbuminuric, and albuminuria and retinopathy were both absent in 29.8% of subjects with reduced eGFR [15]. In subsequent cross-sectional analyses of the NHANES data, higher adjusted prevalence rates (~ 50%) for the non-albuminuric phenotype among individuals with reduced eGFR were observed [8]. Similar findings have been observed in cohorts of type 2 DM patients outside the U.S. and in those enrolled in multicenter multinational interventional studies [16].

Currently there are no large trials that have been performed in non-albuminuric 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 acute kidney injury (AKI) in non-albuminuric patients [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 non-albuminuric patients, though 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 < 30 mL/min per 1.73 m², although such studies are being conducted [19]. The increasing prevalence of non-
albuminuric or minimally-albuminuric DKD underscores the need to develop new therapies for non-
albuminuric DKD, particularly in those patients with advanced CKD.

Non-albuminuric DKD is thought to be predominantly due to vascular and tubulo-interstitial lesions, and
decline in renal function in such patients may be at least in part 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 which increase systemic and intraglomerular pressure
(hemodynamic theory) in genetically-predisposed patients.. Nearly three decades ago, Hagesawa et al.
initially suggested based on studies in diabetic animals that proinflammatory cytokines might be
involved in the pathogenesis of DKD [20]. The source of cytokine production by the kidneys in DM is
from both infiltrating macrophages and resident kidney cells. Production of reactive oxygen species
(ROS), pro-inflammatory factors, and certain growth factors (such as transforming growth factor-beta)
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. 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 [22]. Various types of renal cells (endothelial, mesangial, epithelial, and tubular cells)
are capable of synthesizing proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α),
interleukin 1 (IL-1), and interleukin 6 (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 macro-vascular 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 type 2 DM patients with mild proteinuria (< 1 g/d), serum concentrations of high-sensitivity C-reactive protein (hs-CRP) 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. found that diabetic rats treated with the chimeric anti-TNF-α antibody infliximab showed a reduction in albuminuria [35].

Proinflammatory interleukins 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 (GBM) 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 non-diabetic rats. Albuminuria was significantly associated with renal mRNA expression of TNF-α and IL-6 but not IL-1 [38]. Another proinflammatory interleukin, IL-18, may also play an important role in DKD [40]. Chronically increased levels of inflammation are associated with an increase in CRP, the latter of which is associated with many pathological conditions in diabetes, including atherosclerosis and DKD [41].

**Targeting Inflammation in DKD**

A role of chronic low-grade inflammation in the microvascular complications in diabetic patients 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 GLP-1 receptor agonists [21]. In addition, three large randomized controlled trials specifically targeting inflammation in DKD have been or are currently being performed.

**Bardoxolone**

s oxidative stress and reduces inflammation by inhibiting pro-inflammatory cytokines, decreasing transforming growth factor-beta and extracellular matrix proteins [44]. The BEACON study using the Nrf2 activator bardoxolone methyl was stopped prematurely due to an increase in adverse cardiovascular outcomes, and thus its role in ESRD 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 endpoint [46]. Bardoxolone is being studied again in Japan in a Phase 3
Study of Bardoxolone Methyl in Patients with Diabetic Kidney Disease; AYAME Study (NCT03550443), with an estimated completion date of March 2022. Patients with \( \text{eGFR} \) 15-60 mL/min/1.73m\(^2\) will be studied. The primary outcome is time to onset of a \( \geq 30\% \) decrease in \( \text{eGFR} \) from baseline or ESRD.

**Selonsertib**

Glucose can activate the transcription factor nuclear factor kappa B (NF-\(k\)B), resulting in increased inflammatory gene expression, in part through oxidative stress, advanced glycation end-products (AGEs), protein kinase C, and mitogen-activated protein kinases (MAPKs). Apoptosis signal–regulating kinase 1 (ASK1) acts as an upstream regulator for the activation of p38 MAPK and c-Jun N-terminal kinase (c-JNK). 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 urine albumin-to-creatinine ratio did not differ between selonsertib and placebo, but exploratory post hoc analyses suggest that selonsertib may slow diabetic kidney disease progression [48]. A phase 3 trial, Efficacy and Safety of Selonsertib in Participants with Moderate to Advanced Diabetic Kidney Disease (MOSAIC) (NCT04026165) is currently enrolling patients with type 2 DM and \( \text{eGFR} \) 20-60 mL/min/1.73m\(^2\) with albuminuria and is estimated to be completed in December 2024. Clinical outcome measures are time to \( \geq 40\% \) decline in \( \text{eGFR} \) from baseline, ESRD, or death due to kidney disease.

**Pentoxifylline**

Phosphodiesterases (PDEs) are a class of enzymes that hydrolyze cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) and are involved in many physiological 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 non-specific inhibition of PDEs. PTX was approved by the United States Food and Drug Administration for the treatment of intermittent claudication more than 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, since 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 cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). PTX inhibits predominantly the PDE3 and PDE4 isoforms and thus primarily affects cAMP. The PTX-induced increase in cAMP will in turn increase protein kinase A (PKA) 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 non-diabetic 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 pro-inflammatory 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 type 2 diabetic patients [63]. The proinflammatory cytokines TNF-α and tumor necrosis factor–like weak inducer of apoptosis (TWEAK) decrease renal Klotho expression mediated by NF-κB [64-66]. In a recent post-hoc analysis of the PREDIAN trial by Navarro-Gonzalez et al., administration of PTX to type 2 diabetic patients with CKD stages 3 and 4 resulted in some reduction of serum and urinary TNF-α and increased serum and urinary Klotho concentrations [67]. 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 utilized a small number of subjects and were of short duration, and all used surrogate endpoints such as reduction in proteinuria and changes in eGFR and not hard endpoints such as ESRD 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 Caucasian patients with type 2 DM and stage 3 or 4 CKD and urinary albumin excretion (UAE) > 30 mg/24 hours. Treatment with PTX (1200 mg/day) decreased proteinuria and urinary concentration of TNF-α and slowed decline in eGFR. At study end, eGFR had decreased by 2.1 mL/min/1.73 m² in the PTX group vs. 6.5 mL/min/1.73 m² (between group difference of 4.3 mL/min/1.73 m², 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), being 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. While these results are very intriguing, there are some limitations to the PREDIAN trial. First, the study enrolled only Caucasian patients. Second, it was a single-center study, which also 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 ESRD and mortality.

The VA Cooperative Study Pentoxifylline in Diabetic Kidney Disease (PTXRx) (NCT03625648) is comparing PTX to placebo in patients with type 2 DM and eGFR 15-60 mL/min/1.73 m², targeting high risk patients according to the K-DIGO “heat map” [83]. Patients will need to have eGFR 15 to less than 30 mL/min/1.73 m², or eGFR 30 to less than 45 mL/min/1.73 m² with urinary albumin-to-creatinine ratio (UACR) > 30 mg/g, or eGFR 45 to less than 60 mL/min/1.73 m² with UACR > 300 mg/g. The primary outcome is time to ESRD 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 (ACEIs/ARBs) 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. reported 8 studies with a total of 587 patients (all diabetic), in which PTX was combined with RAAS blockers [86]. Addition of PTX resulted in further reductions in albuminuria and proteinuria and urinary TNF-α but did not result in significant changes in glycated hemoglobin (HbA1c), serum creatinine, creatinine clearance, systolic blood pressure, or diastolic blood pressure. Jiang et al. reported 12 trials with 613 participants (most included only diabetic patients) [87]. PTX significantly decreased proteinuria compared to the placebo or no-treatment groups and led to a lesser decline of eGFR. There were no significant differences in blood pressure 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 as 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 endpoints such as ESRD and death. Such a trial is currently being conducted (www.clinicaltrials.gov, Pentoxifylline in Diabetic Kidney Disease (PTXRx)), but the results will not be available for several years. At the current 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 ≤60 mL/min/1.73m² 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.
Disclosures

D Leehey has nothing to disclose.

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Author Contributions

D Leehey: Conceptualization; Project administration; Resources; Software; Writing - original draft;

Writing – review and editing
References


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<table>
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<tr>
<th>Study</th>
<th>Duration</th>
<th>Entry Criteria</th>
<th>Groups</th>
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<th>Intervention</th>
<th>Placebo-controlled</th>
<th>Outcome</th>
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<td>Aminorroaya Nephron Clin Pract 2005;99:c73–c77</td>
<td>2 mo.</td>
<td>Type 2 DM UPE &gt; 300 mg/24h</td>
<td>PTX vs. captopril</td>
<td>39</td>
<td>PTX 1200 mg/d</td>
<td>No</td>
<td>Decrease in UPE in both groups. (PTX: 29% reduction, p &lt; 0.05; captopril 38% reduction, p &lt; 0.01)</td>
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<td>Ghorbani Nefrologia 2012; 32:790-6</td>
<td>6 mo.</td>
<td>Persistent UPE &gt; 150 mg/24h despite RAAS blockers</td>
<td>PTX + losartan and enalapril vs. losartan and enalapril</td>
<td>100</td>
<td>PTX 400 mg/d</td>
<td>No</td>
<td>Decrease in UPE (PTX: 69% reduction, p &lt; 0.001; Control: 16% reduction, pNS) Increase in creatinine clearance (PTX: 5.9% increase, Control: 0.7% decrease, p = 0.04)</td>
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<td>Guerrero-Romero Clin Nephrol 1995; 43:116-21</td>
<td>4 mo.</td>
<td>Type 1 and type 2 DM with overt proteinuria</td>
<td>PTX vs. placebo</td>
<td>86</td>
<td>PTX 1200 mg/d</td>
<td>Yes</td>
<td>Decrease in UPE (Type 1: PTX: 86% reduction, p &lt; 0.01; Placebo: 7% reduction, pNS; Type 2: PTX: 93% reduction, p &lt; 0.001; Placebo: 6% increase, p = 0.012)</td>
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<td>Han Diabetol Metab Syndr 2015; 7:64</td>
<td>6 mo.</td>
<td>Type 2 DM UACR &gt; 30 mg/g</td>
<td>PTX vs. placebo</td>
<td>174</td>
<td>PTX 1200 mg/d</td>
<td>Yes</td>
<td>Decrease in UACR (PTX: 23% reduction, Placebo: 4% reduction; p = 0.012)</td>
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<td>Harmankaya Ren Fail 2003; 25: 465-70</td>
<td>9 mo.</td>
<td>Type 2 DM Persistent microalbuminuria</td>
<td>PTX + lisinopril vs. lisinopril</td>
<td>50</td>
<td>PTX 600 mg/d</td>
<td>No</td>
<td>Decrease in UAE (PTX: 42% reduction, p &lt; 0.05, Control: 35% reduction, p &lt; 0.05)</td>
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<td>Navarro-Gonzalez JASN 2015; 26:220-9</td>
<td>24 mo.</td>
<td>Type 2 DM stage 3-4 CKD Urine albumin excretion &gt; 30 mg/24h</td>
<td>PTX and ACEi or ARB vs. ACEi or ARB</td>
<td>169</td>
<td>PTX 1200 mg/d</td>
<td>No</td>
<td>Decrease in UAE (PTX: 14.9% reduction; Control: 5.7% increase, p = 0.001) Decrease in eGFR decline (PTX: 2.1 mL/min/1.73 m²; Control: 6.5 mL/min/1.73/m², p &lt; 0.001)</td>
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<tr>
<td>Navarro Diabetes Care 1999; 22: 1006-8</td>
<td>6 mo.</td>
<td>DM (type not stated) with creatinine clearance &lt; 35 mL/min</td>
<td>PTX vs. standard Rx</td>
<td>24</td>
<td>PTX 400 mg/d</td>
<td>No</td>
<td>Decrease in UPE (PTX: 59% reduction, p &lt; 0.05; Control: pNS)</td>
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Table 1. Renal Effects of PTX in Clinical Trials
<table>
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<th>Study</th>
<th>Duration</th>
<th>Type of Diabetes</th>
<th>Proteinuria Criteria</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>N</th>
<th>Outcome</th>
<th>p-value Details</th>
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<td>Navarro Am J Kidney Dis 2003; 42:264-70</td>
<td>4 mo.</td>
<td>Type 2 DM</td>
<td>Proteinuria &lt; 3 g/d</td>
<td>PTX and ACEi or ARB vs. ACEi or ARB</td>
<td>45</td>
<td>PTX 1200 mg/d</td>
<td>No</td>
<td>Decrease in UPE (PTX: 15% reduction, p &lt; 0.001; Control: 0.5% reduction, pNS)</td>
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<tr>
<td>Navarro JASN 2005; 16: 2119-26</td>
<td>4 mo.</td>
<td>Type 2 DM</td>
<td>UAE &gt; 300 mg/24h, Normal renal function</td>
<td>PTX and ARB vs. ARB</td>
<td>61</td>
<td>PTX 1200 mg/d</td>
<td>No</td>
<td>Decrease in UAE (PTX: 17% reduction; Control: 5.5% reduction, p &lt; 0.001)</td>
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<tr>
<td>Oliaei Caspian J Intern Med 2011; 2:309-13</td>
<td>3 mo.</td>
<td>Type 2 DM</td>
<td>Proteinuria &gt; 500 mg/d</td>
<td>PTX + ACEi or ARB vs. ACEi or ARB</td>
<td>56</td>
<td>PTX 1200 mg/d</td>
<td>Yes</td>
<td>Decrease in proteinuria (PTX: 61% reduction; Placebo: 20% reduction, p &lt; 0.001)</td>
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<td>Rodriguez- Moran Clin Nephrol 2005; 64: 91-7</td>
<td>6 mo.</td>
<td>Type 2 DM UAE &gt; 20-200 mcg/min, No RAAS blockers</td>
<td>PTX vs. captopri</td>
<td>130 PTX 1200 mg/d</td>
<td>No</td>
<td>Equivalent decrease in UAE (PTX: 77% reduction, Captopril: 76% reduction, pNS)</td>
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<tr>
<td>Rodriguez- Moran Clin Nephrol 2006; 66: 3-10</td>
<td>16 wks.</td>
<td>Type 2 DM UAE &gt; 200-200 mcg/min, No RAAS blockers</td>
<td>PTX vs. placebo</td>
<td>40 PTX 1200 mg/d</td>
<td>Yes</td>
<td>Decreased UAE (PTX: 74% reduction, p = 0.02; Placebo: 7% reduction, pNS)</td>
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<td>Roozbeh Ren Fail 2010; 32:172-8</td>
<td>6 mo.</td>
<td>Type 2 DM</td>
<td>UPE &gt; 500 mg/d</td>
<td>PTX + captopril vs. captopril</td>
<td>70</td>
<td>PTX 1200 mg/d</td>
<td>No</td>
<td>Decrease in UPE (PTX: 56% reduction, Placebo: 28% reduction, p = 0.007)</td>
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<td>Shahidi Int J Nephrol 2015; 2015:259592</td>
<td>6 mo.</td>
<td>Type 2 DM w microalbuminuria</td>
<td>PTX vs. placebo</td>
<td>40 PTX 1200 mg/d</td>
<td>Yes</td>
<td>No difference in UACR, BP, or eGFR (PTX: 2.2% reduction in UACR, Placebo: 1.2% increase in UACR, pNS)</td>
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<tr>
<td>Solerte Acta Diabetol Lat 1987; 24: 229-39</td>
<td>12 mo.</td>
<td>Type 1 DM</td>
<td>UPE &gt; 500 mg/d</td>
<td>PTX vs. conventional Rx</td>
<td>21</td>
<td>PTX 1200 mg/d</td>
<td>No</td>
<td>Decrease in UPE (PTX: 47% reduction, p &lt; 0.01; Conventional: 42% reduction, p &lt; 0.01) Increase in creatinine clearance (PTX: 20% increase, p &lt; 0.01; Conventional: 14% increase, p &lt; 0.01)</td>
</tr>
</tbody>
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UPE = urine protein excretion; UAE = urine albumin excretion; UACR = urinary albumin to creatinine ratio
Figure Legend

Figure 1. PTX inhibits PDE activity increasing cAMP levels that activates PKA. Active PKA would inhibit ubiquitination that drives IκBα to 26S proteasome degradation and p50/p65 activation of the expression of cytokines and other genes. Decreased levels of TNF and TWEAK increases KL expression, whereas KL inhibits the production of pro-inflammatory cytokines and TNF-induced adhesion molecules.

PTX; pentoxyfilline; PDE, phosphodiesterase; ATP, adenosine triphosphate; AC, adenylate cyclase; cAMP, cyclic adenosine-3,5-monophosphate; aPKA, active protein kinase A; IκBα, inhibitor of kappa B α; p50 (NF-κB1), nuclear factor NF-kappa-B p50 subunit (nuclear factor kappa-light-chain-enhancer of activated B cells 1); p65 (RelA), nuclear factor NF-kappa-B p65 subunit (V-Rel Avian Reticuloendotheliosis Viral Oncogene Homolog A); TNF, tumor necrosis factor α; IL, interleukin; IFNG, interferon gamma; ICAM1, intercellular adhesion molecule 1; VCAM1, vascular cell adhesion molecule 1; CRP, C reactive protein; TWEAK, TNF-related weak inducer of apoptosis; KL, Klotho.
