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Repurposing drugs for highly prevalent diseases: pentoxifylline, an old drug and a new opportunity for diabetic kidney disease

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ABSTRACT

Diabetic kidney disease is one of the most frequent complications in patients with diabetes and constitutes a major cause of end-stage kidney disease. The prevalence of diabetic kidney disease continues to increase as a result of the growing epidemic of diabetes and obesity. Therefore, there is mounting urgency to design and optimize novel strategies and drugs that delay the progression of this pathology and contain this trend. The new approaches should go beyond the current therapy focussed on the control of traditional risk factors such as hyperglycaemia and hypertension. In this scenario, drug repurposing constitutes an economic and feasible approach based on the discovery of useful activities for old drugs. Pentoxifylline is a nonselective phosphodiesterase inhibitor currently indicated for peripheral artery disease. Clinical trials and meta-analyses have shown renoprotection secondary to anti-inflammatory and antifibrotic effects in diabetic patients treated with this old known drug, which makes pentoxifylline a candidate for repurposing in diabetic kidney disease.

Keywords: diabetes, diabetic kidney disease, pentoxifylline, repurposing

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DIABETIC KIDNEY DISEASE, AN INCREASING PROBLEM

Diabetes mellitus (DM) is a world epidemic that affects >425 million people according to the International Diabetes Federation [1]. Recent estimates from this organization predict a prevalence of >630 million people with DM by the year 2045 [1]. One of the most relevant complications of DM is diabetic kidney disease (DKD) which occurs in >40% of diabetic patients, with no difference between patients with type 1 or type 2 DM [2–4]. Metabolic and haemodynamic insults drive the pathophysiology of DKD causing the deterioration of kidney functions. Until recently, chronic kidney disease (CKD) derived from DM was diagnosed as diabetic nephropathy, which begins with microalbuminuria, followed by a gradual decline in kidney function and overt macroalbuminuria. However, the report of patients with DM and impaired renal function without albuminuria has led to the concept of DKD. DKD is defined as CKD with diabetes being partially involved in the pathogenesis of kidney disease, encompassing the concept of classical diabetic nephropathy [5–8]. Despite advances in therapeutics, healthcare structures and overall population health, DKD is the single most common cause of end-stage kidney disease (ESKD) [9, 10]. Patients with DKD present 20–40 times higher cardiovascular morbidity and mortality rates than patients with DM without kidney impairment; in fact, most patients with DKD die from cardiovascular disease before they start renal replacement therapy.

As a consequence of the ever-growing epidemic of diabetes and obesity, the absolute number of people with ESKD continues to rise [11]. This situation has made the prevention and treatment of DKD a global challenge and a threat to human health and mortality, with a significant social and economic burden [12, 13]. At present, there are no specific therapeutic strategies for DKD, which makes finding new approaches a formidable challenge for the scientific community, since simple control of risk factors is insufficient to cope with disease progression. In search for new therapies, researchers have explored several drug-repurposing opportunities [14].

The pathogenesis of DKD comprises metabolic (hyperglycaemia, dyslipidaemia) and haemodynamic (glomerular hypertension) perturbations which, together, cause mesangial expansion, impairment of endothelial cell function and loss of podocytes in the glomerulus and interstitial fibrosis in the tubular compartment [15–17]. However, the full pathogenesis of the disease remains to be understood, and specific therapeutic targets have not been determined. Current practice guidelines are focussed on halting or delaying the progression of DKD through nonspecific multidisciplinary therapeutic approaches based on an adequate metabolic control and in the control of blood pressure with the renin-angiotensin system (RAS) blockade as a cornerstone therapy [18, 19]. Although this approach improves the systemic blood pressure as well as intraglomerular pressure, a key driver of albuminuria and CKD progression and also decreases kidney inflammation and fibrosis [20, 21], it does not generally halt the progression to ESKD. Moreover, the combination of RAS blockers such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) did not improve monotherapy results and is associated with adverse events including hyperkalaemia, acute kidney injury and hypotension [22–25]. Importantly, sodium-glucose cotransporter 2 inhibitors (SGLT2i) have been recently added to these multidisciplinary treatments, as drugs of choice for DKD treatment [26]. Although the evidence demonstrates renoprotection with the use of SGLT2i on top of RAS blockade, patients with DM continue to suffer from kidney disease and a high percentage of them progress to ESKD. Therefore, there is a need to evaluate new strategies to improve kidney function, delay the progression of the disease and eventually improve kidney survival. These new therapeutic approaches become even more necessary if we consider that recent trials designed to find effective renoprotection in DM patients have failed or were prematurely stopped because of safety concerns; i.e. ruboxistaurin and sulodexide failed to show clear-cut renoprotection in patients with type 2 DM and clinical trials with avosentan and bardoxolone methyl were prematurely terminated because of serious safety concerns [25, 27–31]. The efforts are focussed on targeting key mechanisms involved in the onset and progression of DKD including hyperglycaemia, oxidative stress [32], inflammation [33] and fibrosis [34].

The drug pentoxifylline is a methyl-xanthine derivative and a nonselective phosphodiesterase inhibitor with anti-inflammatory, antiproliferative and antifibrotic actions currently indicated for peripheral artery disease. Clinical trials and meta-analyses have shown renoprotection secondary to anti-inflammatory and antifibrotic effects in diabetic patients treated with pentoxifylline when added to RAS blockade, making pentoxifylline a potential candidate for repurposing in DKD [35].

EMERGING THERAPIES AND POTENTIAL REPURPOSED DRUGS IN DKD

In recent years, promising nephroprotective therapeutic strategies have arisen with the use of new antidiabetic drugs on top of RAS blockade. As discussed above, the current main pharmacological agents in DKD are RAS blockers and SGLT2i. SGLT2i are anti-hyperglycaemic agents that block glucose reabsorption by SGLT2 channels at proximal tubules, thereby stimulating glucosuria and decreasing blood glucose levels in an insulin-independent fashion [36]. But, beyond glycaemic control, secondary outcome analyses in cardiovascular safety randomized controlled trials (RCTs) in type 2 DM patients have shown improved kidney outcomes in patients with CKD [26, 37, 38]. As a result of this evidence, recent consensus documents have placed SGLT2i as antidiabetic drugs of choice on top of RAS blockade for type 2 DM patients with evidence of kidney disease [39, 40]. Despite this success, renal decline still continues in many individuals with diabetes and incident or worsening nephropathy occurs in 12.7% of individuals treated with empagliflozin [37] and new treatments are needed.

The unexpected nephroprotective success of SGLT2i in DKD has not been replicated and a large number of drugs, even with added RAS blockade, have failed [41]. New drug candidates include the groups of steroidal and nonsteroidal mineralocorticoid receptor antagonists (MRA). MRAs exert antihypertensive actions by suppressing the action of aldosterone, the end product of RAS, and has been reported to decrease proteinuria [42–47]. Two groups of anti-diabetic drugs that could present nephroprotective effects, possibly independently of the glycaemic control, are the glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RA) and the dipeptidyl peptidase-4 (DPP-4) inhibitors [48, 49]. These incretin-based drugs decrease albuminuria in DKD patients, but controversy persists over their potential to slow the rate of estimated glomerular filtration rate (eGFR) decline [50–59].

The effectiveness of inhibiting advanced glycation end product (AGE) accumulation has been also conducted. AGE accumulation in kidney samples correlates with DKD progression and, at present, the administration of AGE inhibitors in DKD patients is the focus of clinical and basic research, with controversial results in a decrease of proteinuria and in the progression of GFR decline [60–63].

With the exception of SGLT2i and finerenone, there have been no new therapies for the treatment of nephropathy in type 2 DM since the approval of irbesartan and losartan by the Food and Drug Administration (FDA) > 15 years ago. There is a desperate need to identify treatments for DKD, and several large-scale trials in people with DKD have been conducted and failed [24, 25, 29, 30]. In this sense, together with new antidiabetic drugs, drug repurposing is an alternative to *de novo* drug discovery, to find promising candidates to treat DKD. Drug repurposing offers multiple advantages, such as an accelerated and inexpensive drug development process. This approach decreases development risks, since the safety of the compound, which is one of the main reasons for high attrition rates, is already well established [35, 64, 65].

The strategy of drug repurposing has been widely employed in recent times during the coronavirus disease 2019 (COVID-19) pandemic, witnessing the evaluation and use of several existing molecules for their therapeutic potential against coronaviruses including hydroxychloroquine, remdesivir, ivermectin, lopinavir/ritonavir, baricitinib, dexamethasone and others [66]. Well-known examples of drug repositioning include thalidomide, which was used to prevent morning sickness and posteriorly repositioned for the treatment of multiple myeloma [67]; minoxidil and finasteride, initially approved for the treatment of hypertension and benign prostate hyperplasia, respectively, were repurposed for the treatment of male pattern baldness.

Methyl bardoxolone is a semi-synthetic triterpenoid with anti-inflammatory effects [68]. Methyl bardoxolone, initially studied for the prevention and treatment of cancer, was repurposed for other diseases with an inflammatory component including DKD following the observation of decreased serum creatinine in cancer patients [69, 70]. These promising results led to the Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes Mellitus: The Occurrence of Renal Events (BEACON NCT01351675) phase III clinical trial [30], which included 2185 participants with type 2 DM. Although this trial was terminated due to serious adverse events originating from high rates of heart failure-related hospitalizations and deaths in patients treated with bardoxolone, *post hoc* analyses showed that the increase in heart failure events was most likely caused by fluid overload in the first 4 weeks after randomization [71]. Moreover, elevated baseline B-type natriuretic peptide (BNP) levels (>200 pg/mL) and a history of hospitalization were identified as the only risk factors for heart failure. Patients without these two risk factors showed the same incidence of heart failure in the bardoxolone methyl and in the placebo groups (2%) [72]. The Phase 2 Study of Bardoxolone Methyl in Patients with Chronic Kidney Disease and Type 2 Diabetes (TSUBAKI, NCT02316821) [73] for the treatment of CKD in Japanese patients without these clinical characteristics, again indicated an increase in the measured GFR in patients treated with methyl-bardoxolone without cases of death or heart failure in any participant.

Other anti-inflammatory agents repurposed for DKD include CCX-140 and bariticinib, both originally developed for rheumatoid arthritis. CCX140-B is an inhibitor of C-C chemokine receptor type 2 (CCR2) that decreases macrophage migration and activation that was repurposed for DKD after the results of a phase II RCT showing kidney-protective effects in patients with type 2 DM when administered on top of standard medication [74]. Administration of baricitinib, which selectively inhibits Janus kinase 1 and 2 (JAK1 and JAK2), has been recently tested in a phase II RCT including 129 DKD patients, finding a decrease in albuminuria [75].

Endothelin A is a vasoactive peptide that exerts vasoconstrictive actions of glomerular afferent and efferent arterioles, crucial determinants of glomerular haemodynamics, which leads to a decrease in GFR [76] and also generates kidney injury via inflammation, endothelial injury, podocyte disruption and fibrosis. Endothelin A receptor antagonists were first evaluated in men with metastatic hormone-refractory prostate cancer [77] and are currently approved for the treatment of pulmonary arterial hypertension [78]. The endothelin A receptor antagonists atrasentan decreases proteinuria in experimental kidney disease [79], which has led to clinical testing in DKD [80–82]. In DKD, atrasentan decreased blood pressure and albuminuria when added to stable RAS blockade, but was associated with fluid overload and heart failure exacerbation [83].

Finally, pentoxifylline has recently been added to this group of potentially repurposed kidney protective drugs based on its anti-inflammatory and antiproteinuric effects. Pentoxifylline is currently indicated for peripheral artery disease, but open-label trials have shown beneficial results in DKD and also in nonspecific CKD and chronic allograft nephropathy. Along with the decrease in albuminuria and inflammation, the deceleration in the GFR decline rate and the preservation of the anti-ageing factor Klotho are the most important findings in DKD patients treated with pentoxifylline [84–86].

PENTOXIFYLLINE IN DKD

An old-new friend

Pentoxifylline [3,7-dimethyl-1-(5-oxohexyl)-3,7-dihydro-1H-purine-2,6-dione] is a promising anti-inflammatory methylxanthine derivative with haemorheological actions. Pentoxifylline was approved by the United States FDA for the treatment of intermittent claudication resulting from peripheral vascular disease >30 years ago [87–89]. This drug decreases blood viscosity, erythrocyte aggregation, erythrocyte rigidity and platelet aggregation. The improvement in red blood cell flexibility and deformability leads to an improved blood flow [89, 90]. The pharmacological properties of pentoxifylline have been frequently revisited, and recent evidence indicates other possible beneficial effects of this old drug [91]. Thus, the repurposing of pentoxifylline has been suggested for treating brain ischaemia, non-alcoholic fatty liver diseases and preserving skeletal muscle function [90].

The haemorheological properties and its potential to decrease intraglomerular pressure led to an early interest in pentoxifylline as a therapeutic agent in kidney disease. In 1982, Blagosklonnaia *et al.* [92] presented the first clinical evidence of kidney protective effects of pentoxifylline. Diabetic patients treated with 300 mg/day of pentoxifylline for 3 weeks improved eGFR and decreased proteinuria. The possible application of pentoxifylline for kidney protection in DKD was recently renewed as studies showed pentoxifylline anti-inflammatory, anti-proliferative and anti-fibrotic effects [93, 94] (Table 1).

A series of five open-label clinical trials conducted between 1999 and 2006 focussed on the potential kidney protective effects of pentoxifylline in DKD (Table 1). First, Navarro *et al.* [95] reported a 42.2 and 59.3% decrease in serum tumour necrosis factor α (TNFα) and proteinuria levels, respectively, in a small

Table 1. Main clinical and experimental studies on the use of pentoxifylline in DKD

Ref.	Type of study	Type of intervention	Population	Treatment	Main effects of PTF
Clinical studies					
[84]	RCT	PTF versus untreated	DM patients, $n = 169$ Albuminuria >30 mg/24 h, eGFR 60–15 mL/min/1.73 m^2	1200 mg/day, 2 years. Background RAS blockade	Improvements in GFR decay and in proteinuria. Decrease of urinary levels of TNFα
[95]	Open-label RCT	PTF versus untreated	DM patients, $n = 24$ Albuminuria >300 mg/24 h; creatinine clearance <35 mL/min	400 mg/day, 6 months	Decrease in proteinuria and TNFα levels
[96]	Open-label RCT	PTF versus captopril	DM patients, $n = 39$ Albuminuria >300 mg/24 h; eGFR >60 mL/min/1.73 m^2	1200 mg/day, 8 weeks	Both PTF and captopril decreased proteinuria
[97]	Open-label RCT	PTF versus captopril	DM patients, $n = 130$ UAE 20–200 μg/min	1200 mg/day, 6 months	Both PTF and captopril decreased proteinuria
[98]	Open-label RCT	PTF versus untreated	DM patients, $n = 61$ Albuminuria >300 mg/24 h; eGFR >90 mL/min/1.73 m^2	1200 mg/day, 4 months. Background RAS blockade	Decrease in serum and urinary TNFα levels. TNFα changes related to UAE
[99]	Double-blind RCT	PTF versus placebo	DM patients, $n = 40$ UAE 20–200 μg/min	1200 mg/day, 4 months	Decrease in urinary levels of high and low molecular weight proteins
[100]	Double-blind RCT	PTF versus placebo	Patients with GN, $n = 18$ proteinuria >500 mg/24 h, mean eGFR 71.2 ± 30.6 mL/min/1.73 m^2	800–1200 mg/day, 6 months. Background RAS blockade	Decrease of proteinuria without affecting GFR
[101]	Open-label, controlled trial	PTF versus untreated	Diabetic GE patients, $n = 14$ Proteinuria >1.5 g/24 h; Cr clearance >15 mL/min	400–800 mg/day, 1 year. Background RAS blockade	PTF did not decrease proteinuria or improved renal function
[102]	Double-blind RCT	PTF versus placebo	CKD patients, $n = 40$ Mean eGFR 29.5 ± 10.1 mL/min/1.73 m^2 Proteinuria >1 g/24 h	800 mg/day, 1 year Background RAS blockade	PTF stabilized GFR. No decrease of proteinuria
[103]	RCT	PTF versus untreated	CKD patients, $n = 91$ albuminuria >300 mg/24 h, eGFR <60 mL/min/1.73 m^2	800 mg/day, 1 year. Background RAS blockade	PTF stabilized GFR. No decrease of proteinuria. Decrease in TNFα, fibrinogen and hsCRP
[104]	RCT	PTF versus untreated	CKD patients, $n = 56$ Proteinuria >500 mg/g of Cr; eGFR 10–60 mL/min/1.73 m^2	400–800 mg/day, 1 year. Background RAS blockade	Decrease of proteinuria and stabilization of GFR. Decrease in TNFα and MCP1 levels
[105]	Prospective trial	All in PTF	Patients with GN; non-diabetic, $n = 17$. Spot proteinuria >1.5 g/g Cr; eGFR 24–115 mL/min/1.73 m^2	800 mg/day, 6 months	Decrease in spot and 24 h proteinuria (g/g Cr) and in MCP-1 levels
[106]	Single-centre retrospective study	PTF versus untreated	CKD patients, $n = 661$ Mean proteinuria 1102 mg/g of Cr, eGFR <45 mL/min/1.73 m^2	400–800 mg/day, 1 year. Background RAS blockade	Better renal outcome in patients with higher proteinuria

Table 1. Continued

Clinical studies					
Ref.	Type of study	Type of intervention	Population	Treatment	Main effects of PTF
[107]	Prospective trial	All in PTF	CAN patients, $n = 17$ UAE 20–200 μg/min, mean eGFR 38 $\pm$ 8 mL/min/1.73 m^2	1200 mg/day, 6 months	Decrease of proteinuria at 3rd month and improved graft survival. Decrease in CD4 + cells bearing TNFα and IL10
[85]	RCT post-hoc analysis	PTF versus untreated	DM patients, $n = 166$ Albuminuria >30 mg/24 h, eGFR 60–15 mL/min/1.73 m^2	1200 mg/day, 2 years. Background RAS blockade	Increments in serum and urine Klotho. Changes in TNFα associated with changes of urinary Klotho

Ref.	Experimental model	Treatment conc.	Main effects of PTF
Experimental studies			
[108]	RAW 264.7 macrophages	100 µg/mL, 1 h before the addition of LPS	Inhibition of endotoxin-induced TNFα synthesis
[109]	Rat model of crescentic GN	Intravenous 0.1 g/kg/day	Suppression of progressive renal injury through inhibition of renal TNFα, ICAM-1, RANTES, MCP-1 and OPN
[110]	Streptozotocin-induced diabetic rat model	Intraperitoneal 25 mg/kg/day	Decrease in renal TNFα and IL6 and amelioration of renal hypertrophy and sodium retention
[111]	Alloxan-induced diabetic rat model	Oral 25, 50 or 100 mg/kg/day	Decrease in renal TNFα and IL6
[85]	Renal tubular cells	4, 40, 200, 400 or 800 µg/mL, 1 h before the addition of albumin	Upregulation and prevention of albuminuria-induced downregulation of expression of Klotho

RCT, randomized controlled trial; PTF, pentoxifylline; DM, diabetes mellitus; CKD, chronic kidney disease; RAS, renin-angiotensin aldosterone system; TNF, tumour necrosis factor; GE, glomeruloesclerosis; GN, glomerulonephritis; GFR, glomerular filtration rate; hsCRP, high sensitivity C-reactive protein; MCP1, monocyte chemoattractant protein 1; ICAM-1, intercellular adhesion molecule-1; OPN, osteopontin; CAN, chronic allograft nephropathy; UAE, urinary albumin excretion.

group of patients with DM and advanced CKD under pentoxifylline treatment (400 mg/day; 6 months) when compared with a control group. Posteriorly, two open-label RCTs conducted by Aminorroaya *et al.* [96] and Rodríguez-Morán *et al.* [97] also reported a decrease in proteinuria in non-hypertensive type 2 DM patients with microalbuminuria comparable with those achieved with ACEI treatment (captopril) after the administration of 400 mg pentoxifylline three times a day (t.i.d.) for 2 (40% in pentoxifylline-group and 38.5% in captopril-group) and 6 months (77.2% in pentoxifylline-group and 76.6% in captopril-group), respectively. In a subsequent randomized, open-label trial, Navarro *et al.* [98] found an additive percentage decrease in proteinuria of 11.2% in those ARB-treated DM patients who also received 1200 mg/day pentoxifylline for 4 months; i.e. patients receiving pentoxifylline. Pentoxifylline treatment also decreased both serum and urinary levels of TNFα, without significant variations in patients exclusively under therapy with ARB. The antiproteinuric effect of pentoxifylline correlated with a decrease in urinary TNFα levels [98]. Finally, a subsequent RCT by Rodríguez-Morán *et al.* [99] newly reported a decrease in the levels of both high and low molecular weight urinary protein excretion (73.8 and 86.4% decrease, respectively) in non-hypertensive microalbuminuric type 2 DM patients treated with 400 mg pentoxifylline (t.i.d. for 16 weeks) not receiving ACEi or ARB therapy. An RCT published by Badri *et al.* [100] showed a 56% decrease in proteinuria in a small group of non-diabetic patients with glomerulonephritis with add-on pentoxifylline therapy to the background RAS blockade without affecting eGFR. Other clinical trials with different study designs, drug dosages and follow-up periods, also examined the kidney protective effects of pentoxifylline with generally inconclusive results. An open-label controlled clinical trial conducted by Diskin *et al.* [101] did not find any additive antiproteinuric effect of pentoxifylline in diabetic glomerulosclerosis patients with a background of ACEI and ARB therapy after 1 year of follow-up. Important concerns of this study are its non-randomized design, the small number of participants (14 patients) and the use of dual RAS blockade, which has important safety concerns [25, 112]. In a double-blind RCT, Perkins *et al.* [102] also found no differences in proteinuria in 40 DKD patients with mild to moderate CKD after 1 year of add-on pentoxifylline therapy to RAS blockade. However, they observed deceleration in renal function decline in the group treated with pentoxifylline when compared with the control group, with a mean difference between groups of 6.0 mL/min/1.73 m^2, and argued that the proteinuria may not always constitute an optimal surrogate outcome parameter in these studies.

To date, the most important RCT evaluating the kidney protective effects of pentoxifylline in DKD is the Pentoxifylline for Renoprotection in Diabetic Nephropathy (PREDIAN) study, published in 2015 by Navarro Gonzalez *et al.* [84]. The study comprised 169 type 2 DM patients with CKD stages 3 and 4 and residual albuminuria despite RAS blockade. After 2 years of follow-up, patients randomized to the active group (1200 mg/day of pentoxifylline on top of RAS blockade) presented a decrease in the rate of progression of kidney disease, with an eGFR mean difference between groups of 4.3 mL/min/1.73 m^2, accompanied by a 14.9% decrease in proteinuria (increased by 5.7% in the control group). The deceleration in the decline of GFR in the pentoxifylline arm began at month 6 and reached statistical significance after 1 year, suggesting that the therapeutic benefit may only be observed in the long term. Moreover, urine TNFα presented a 10.6% decrease in the pentoxifylline group, with no changes in the control group.

At present, the identification of the central role of inflammation in the development and progression of CKD and its possible therapeutic targets constitutes an important field of research for nephrologists. The anti-inflammatory actions elicited by pentoxifylline have been related to antialbuminuric effects [93, 113–118]. In this regard, an antiproteinuric or kidney function preservation effect of pentoxifylline has also been found in non-diabetic subjects. Goicoechea *et al.* [103] reported stabilization of kidney function and a significant decrease in markers of inflammation, such as TNFα, fibrinogen and high sensitivity C-reactive protein (CRP; a 45.5, 11.1 and 57.4% decrease, respectively) in patients with stage 3 CKD or higher who received pentoxifylline therapy when compared with those exclusively on RAS blockade. Proteinuria did not decrease in the pentoxifylline group, although there was a drop-out and incomplete follow-up rate. Lin *et al.* [104] found that pentoxifylline on top of ARB background therapy stabilized GFR and decreased proteinuria (−23.9%) in macroalbuminuric CKD stage 3 patients after 1 year of follow-up as compared with ARB monotherapy, for whom proteinuria increased 13.8%. Moreover, pentoxifylline decreased urinary levels of TNFα and monocyte chemoattractant protein 1 (MCP-1) (TNFα: 42.8% versus 18.8% and MCP-1: −28.9% versus 6.2%, for pentoxifylline and control groups, respectively). A decrease in both parameters was directly related to the change in proteinuria in the pentoxifylline group. Chen *et al.* [105] reported that 800 mg/day pentoxifylline for 6 months decreased proteinuria in 17 patients with primary glomerular diseases [36.5% and 33.9% decrease in spot and 24 h proteinuria (g/g Cr)]. This decrease was associated with a decline in urinary mean percentage decrease of 46% in MCP-1 urinary excretion levels. In a larger study, Chen *et al.* published a retrospective analysis of a study comprising 661 patients with CKD stages 3–5 treated with pentoxifylline [106]. Again, pentoxifylline on top of RAS blockade had kidney protective effects in the subset of patients with higher levels of proteinuria. A trial conducted by Shu *et al.* [107] reported a 19.6% decrease in proteinuria in third month and improved graft survival by the end of the study in non-diabetic renal transplant recipients with chronic allograft nephropathy and microalbuminuria treated with pentoxifylline for at least 6 months.

Two recent meta-analyses reported the effects of pentoxifylline alone or in combination with other treatments in the decrease in proteinuria and in the preservation of kidney function in patients with diabetic or non-diabetic CKD. In the first meta-analysis, Leporini *et al.* [119] concluded that pentoxifylline was effective in decreasing proteinuria compared with control, a benefit that was more evident in patients with type 1 DM, higher proteinuria at baseline and early renal impairment. They also found an improvement in renal function (eGFR/creatinine clearance) in the long-term and in patients with more advanced CKD. In the second meta-analysis, Liu *et al.* [120] concluded that pentoxifylline in combination with RAS blockade decreases proteinuria and slows down the decline of renal function in patients with CKD stages 3–5.

Finally, an analysis of a nationwide administrative dataset of advanced CKD patients identifying two propensity score-matched cohorts (pentoxifylline users and nonusers) reported that the pentoxifylline group was protected from ESKD [121] This was the first evidence of the ability of pentoxifylline in decreasing the risk of ESKD even in patients with advanced CKD.

Mechanisms of kidney protection by pentoxifylline

Pentoxifylline is a methyl-xanthine derivative with several effects including the non-selective inhibition of phosphodiesterases (PDEs). The balance of intracellular cyclic adenosine-3,5-monophosphate (cAMP), an important intracellular second

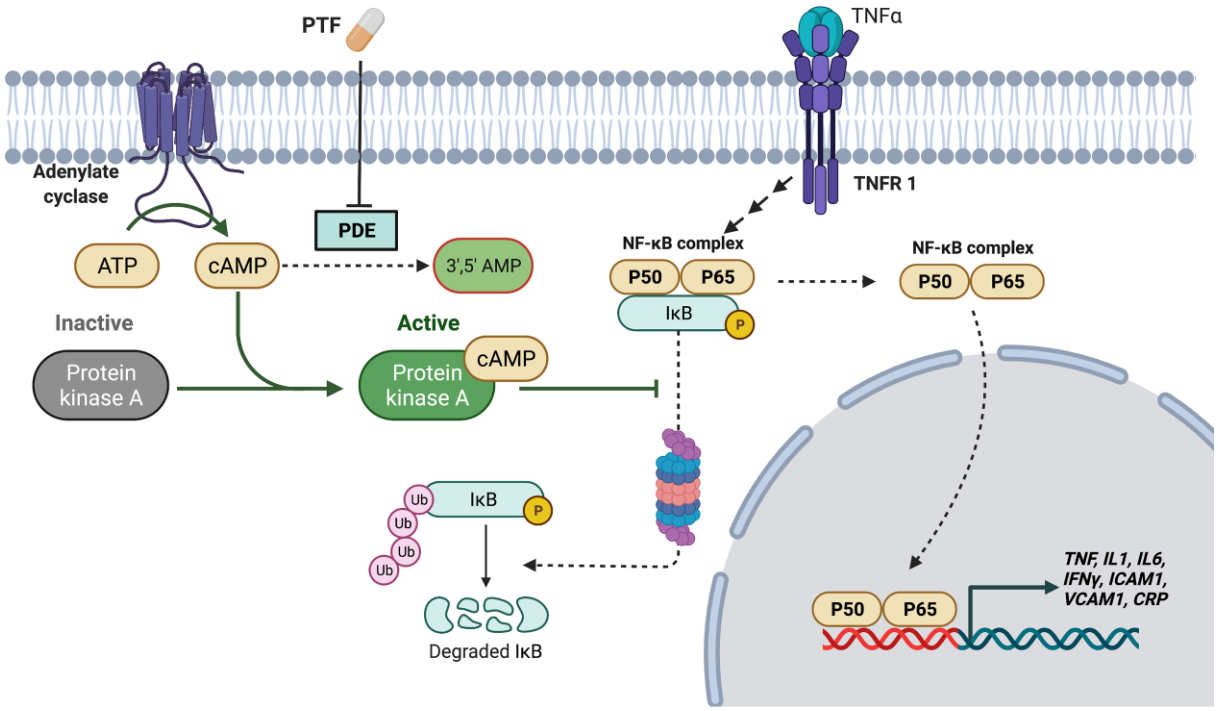

FIGURE 1: Mechanism proposed to explain the anti-inflammatory effects of pentoxifylline. The inhibition of PDE exerted by pentoxifylline increases cAMP levels activating PKA. Active PKA would inhibit ubiquitination that drives IkB to proteasome degradation preventing thus p50/p65 translocation and the expression of inflammatory cytokines and other genes. Dashed lines, inhibition; PTF, pentoxifylline; PDE, phosphodiesterase; ATP, adenosine triphosphate; AC, adenylate cyclase; cAMP, cyclic adenosine-3,5-monophosphate; IkB, inhibitor of kappa B; TNF, tumour necrosis factor α; IL, interleukin; IFN, interferon; ICAM1, intercellular adhesion molecule 1; VCAM1, vascular cell adhesion molecule 1; CRP, C-reactive protein.

signalling messenger, is mainly dependent on the activity of two enzymes: adenylyl cyclase, which plays a major role in cAMP synthesis and PDEs, which hydrolyze cAMP [122, 123]. Therefore, the inhibition of PDEs by pentoxifylline prevents the degradation of cAMP (Fig. 1). High cAMP levels in turn promote protein kinase A (PKA) activation leading to the phosphorylation of diverse effectors followed by inhibition of signalling pathways involved in proteinuria and renal fibrosis [124–126].

PDEs have emerged as promising targets for pharmacological intervention against CKD progression [127–129]. Mammalian cells have 11 gene families (PDE1–PDE11) and each family encompasses 1–4 distinct genes, giving >20 genes in mammals encoding >60 different PDE isoforms. *In vitro*, pentoxifylline inhibits PDE3 and/or PDE4 isozymes through a PKA-dependent pathway [124, 126, 130]. Importantly, PDE3 and PDE4 isozymes are mainly expressed in monocytes and neutrophils [131–133], which makes them a therapeutic target in many inflammatory diseases, including asthma, chronic obstructive pulmonary disease, inflammatory bowel disease, psoriasis, nervous system inflammation and rheumatoid arthritis [133]. Pentoxifylline presents anti-inflammatory properties mediated by the inhibition of PDEs that supports its potential application in the kidney protection of the patient with DM [113–118]. In experimental models, pentoxifylline modulates signalling pathways or components triggered by inflammatory cytokines. *In vitro*, pentoxifylline inhibits endotoxin-induced TNFα synthesis in RAW 264.7 macrophages [108]. Pentoxifylline also inhibited endotoxin-induced TNFα production both in the serum of mice and in cultured adherent peritoneal exudate cells [93]. In a rat model of crescentic glomerulonephritis, pentoxifylline exerts anti-inflammatory and immunomodulatory actions through the inhibition of renal TNFα, ICAM-1, RANTES, MCP-1 and OPN, thereby suppressing progressive renal injury [109]. Similarly, pentoxifylline decreases the renal expression of pro-inflammatory cytokines including TNFα and IL6 in streptozotocin- or alloxan-induced diabetic rat models [110, 111], ameliorating renal hypertrophy and sodium retention [110]. Clinical trials evaluating the anti-inflammatory properties of this drug in non-diabetic patients report considerable modulating effects on the production of inflammatory cytokines and adhesion molecules in patients with coronary artery disease and atherosclerosis [134, 135]. Similarly, pentoxifylline decreased TNFα and interferon-gamma T-cell expression in ESKD patients [136].

As discussed above, most RCTs evaluating the renal effects of pentoxifylline in patients with DM have shown kidney protection, evidenced by the decrease in proteinuria and, in some cases, the improvement or preservation of GFR (Fig. 2). Importantly, some RCTs also observed a significant decrease in inflammatory parameters. The antiproteinuric effect of pentoxifylline has been associated with a significant decrease in TNFα levels [95, 99]. Similarly, clinical trials conducted in CKD patients with stage 3 or higher reported stabilization of renal function and decreased circulating levels of TNFα, fibrinogen and CRP after treatment with pentoxifylline [118] and a decrease in proteinuria and urinary levels of TNFα and MCP1 after 1 year on add-on pentoxifylline to ARB background therapy [104]. The PREDIAN trial [84] evaluated the kidney-protective effects of pentoxifylline in DKD patients under RAS blockade. After 2 years, patients on pentoxifylline presented a decrease in the progression of renal disease that was accompanied by a decrease in proteinuria and urinary levels of TNFα. Two meta-analyses also pointed to the decrease of proinflammatory cytokines production as the most likely

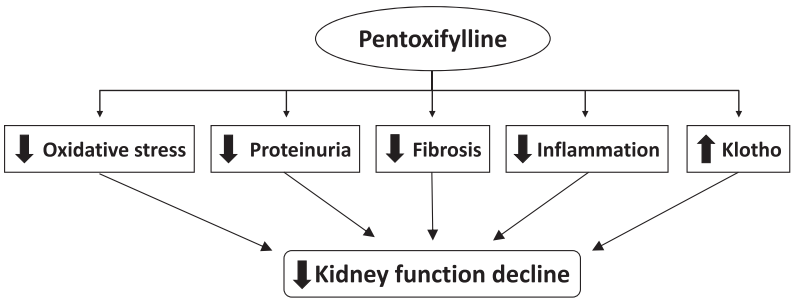

FIGURE 2: Proposed beneficial effects of pentoxifylline on kidney function in DKD patients.

explanation for this antiproteinuric effect in DKD patients [137] and concluded that pentoxifylline additively decreases proteinuria and TNFα in DKD patients receiving RAS inhibitors [138].

An unexpected beneficial effect of pentoxifylline in DKD patients could be the stimulation of factors that promote kidney health [139]. The protein Klotho is an important regulator of mineral metabolism mainly expressed in kidney tubular epithelial cells and, to a lesser extent, in parathyroid glands, choroid plexus of the brain, vascular tissue and peripheral blood cells [140, 141]. Two forms of Klotho can be found: a single-pass transmembrane protein and a soluble form generated from proteolytic cleavage of the extracellular domain of the membrane-bound form [142]. Soluble Klotho is found in the cerebrospinal fluid, urine and blood, and declines in CKD patients with the progression of the disease. Klotho has anti-ageing and kidney-protective effects. In fact, specific epigenetic prevention of Klotho downregulation prevented acute kidney injury in mice [143]. Interestingly, patients with type 2 DM also have lower soluble Klotho levels [144, 145] and kidney Klotho is decreased in biopsies from patients with early stages of DKD [146]. Taken together, these data point to the potential utility of Klotho as an early biomarker of renal impairment in type 2 DM patients and to Klotho downregulation as a driver of DKD progression [147]. Moreover, Klotho has been inversely related to inflammation. Pro-inflammatory cytokines like TNFα and TWEAK (tumor necrosis factor-like weak inducer of apoptosis) inhibit renal Klotho expression in an NF-κB-mediated manner *in vivo* and *in vitro* [148–151]. Clinical translation of this observation is supported by a *post-hoc* analysis of the PREDIAN trial [84]. Administration of pentoxifylline to type 2 DM patients with CKD stages 3 and 4 decreased serum and urinary TNFα and increased serum and urinary Klotho levels [85]. Even though the precise mechanisms are unknown, a feasible hypothesis is that the stimulation of Klotho production by pentoxifylline may result from its anti-inflammatory properties, although in cultured tubular cells, pentoxifylline directly prevented the albuminuria-induced downregulation of Klotho expression [85, 152]. Moreover, pentoxifylline increased tubular cell Klotho above baseline levels, suggesting that promoting kidney expression may be one of the mechanisms of kidney protection by pentoxifylline. Moreover, a recently published experimental study, confirmed the positive effect of therapeutic doses of pentoxifylline (10 μg/mL) on Klotho expression in RAW 264.7 cells, showing that this up-regulation is not limited to kidney cells [153].

CONCLUSIONS AND FUTURE PERSPECTIVES

The global burden of diabetes is predicted to increase dramatically in the coming decades in parallel with the rising of obesity. One of the most important complications of diabetes is DKD, which substantially increases cardiovascular morbidity and mortality, determining a considerable impairment in the quality of life. Indeed, CKD is set to become the fifth global cause of death by 2040 [154]. In a recent large, retrospective cohort study including 65 000 adults with type 2 DM and CKD, a high proportion (10%–17%) of patients presented disease progression over a median follow-up of only 2 years [153]. Previous studies also indicated that DM is a more frequent cause of accelerated progression from CKD to ESKD compared with other predictors including proteinuria, heart failure, anaemia and elevated systolic blood pressure [155].

Even with the widespread use of SGLT2i and GLP-1 receptor agonists, a substantial residual risk of DKD progression remains. Therefore, there is a need to find new therapeutic targets and strategies. Pentoxifylline constitutes a potential repurposed drug for the treatment of DKD. Although the repurposing of pentoxifylline constitutes a promising opportunity in providing a low-cost access to a feasible therapy in DKD, various challenges remain. A recent study reported an increased risk of major bleeding events in CKD patients on pentoxifylline treatment [156]. This population carries a higher risk of bleeding due to the presence of platelet dysfunction and anaemia, especially in patients with albuminuria [157, 158].

As pointed out by Leporini *et al.* [119] in a systematic review and meta-analysis aimed at evaluating the benefits of pentoxifylline on renal outcomes in CKD patients, whether this drug may be useful for retarding disease progression remains partly unanswered for definite reasons. One of them is the heterogeneity of the studies with respect to sample sizes, doses of pentoxifylline, poblation in the study (CKD stage and aetiology, proteinuria levels) and control groups and concomitant RAS blocking treatments. Most RCTs were of low methodological quality and carried out with small sample sizes and only provided short-term data for surrogate kidney function endpoints such as eGFR or serum creatinine, proteinuria and albuminuria.

Future studies with longer follow-up, larger sample size and including hard clinical outcomes are needed. To our knowledge, at present, there are two phase IV clinical trials evaluating the effects of pentoxifylline in the progression of DKD patients. The Veterans Affairs (VA) PTXRx (NCT03625648) is a double-blind, placebo-controlled, multicentre RCT designed to evaluate the utility of pentoxifylline, when added to usual care, in the decrease in the incidence of ESRD or death in patients with type 2 diabetes with DKD [159]. The enrolment of patients for this study (which is estimated in 2510 participants) began in 2019 and the primary completion date will be at the beginning of 2028. The second clinical trial in course, PENFOSIDINE (Pentoxifylline

Effect in Patients With Diabetic Nephropathy, NCT03664414), began in 2018. PENFOSIDINE included 196 patients with DKD and the objectives included evaluating the antioxidant, anti-inflammatory and antifibrotic effects of receiving pentoxifylline (400 mg/three times a day) for a period of 2 years. The results of these trials will shed light on the long-term effects of pentoxifylline on various markers of inflammation, oxidative stress and fibrosis, on surrogate markers of renal function such as a decrease in proteinuria and changes in eGFR and on hard endpoints such as ESRD and death.

In any case, an important problem that faces the repurposing of many drugs, including pentoxifylline, is the absence of exclusivity for the industry. Since pentoxifylline was approved for intermittent claudication, no studies were conducted about its utility for other diseases prior to the approval or before the expiration of the patent. This implies that funding for future research is highly compromised even though current research may demonstrate the efficacy of pentoxifylline in other diseases. Pharmaceutical companies find it less lucrative redirecting resources towards repurposing programmes given the lack of standardized regulations ensuring market protection. Moreover, even after marketing approval, the off-label and unlicensed prescription of a generic version of this old drug leaves little or no space for profit for the industry. Therefore, pivotal RCTs in search of a DKD indication for pentoxifylline should be funded by government-supported trial programmes.

In addition, a successful new indication of the repurposed drug requires extensive knowledge of the pathogenesis of the target disease, as well as the postulated mechanism of action of the drug. Present data point to the ability of pentoxifylline to slow CKD progression when macroalbuminuria is present, even in advanced stages of DKD with maximized RAS blocker therapy. However, although there is evidence for an anti-inflammatory effect, the precise mechanism for the beneficial effect is not known and may also involve increasing Klotho production. In fact, the pathogenic pathways for DKD are poorly understood, as exemplified by the poor therapeutic toolkit and low-grade inflammation is just one of the interrelated contributing mechanisms along with hyperglycaemia, altered lipid metabolism, RAS hyperactivation and increased sympathetic activity. In any case, an in-depth study of the hidden therapeutic potential of pentoxifylline and its repurposing for the DKD new indication offers a tremendous hope to decrease residual kidney risk and prevent the growth of the DKD pandemic.

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CONFLICT OF INTEREST STATEMENT

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