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THERAPEUTIC EFFICACY OF PENTOXIFYLLINE ON PROTEINURIA AND RENAL PROGRESSION IN DIABETIC AND NON DIABETIC PATIENTS

Pharmaceutical Science

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ABSTRACT

Proteinuria is a prevalent issue in individuals with chronic kidney disease (CKD); ACEI/ARBS, which regulate blood pressure, simply delays the illness's progression; it does not halt it. One medication that both slows and reverses the progression of chronic kidney disease to end stage renal failure is pentoxifylline. This article emphasizes PTX's anti-proteinuric properties. It possesses a number of medicinal qualities, including as anti-fibrotic, anti-inflammatory, and anti-proliferative effects. According to the findings of the numerous trials, PTX monotherapy stops the development of CKD. Additionally, PTX and ACEI/ARBS work synergistically to greatly decrease proteinuria. Add-on PTX treatment with RAS blocking reduces the amount of glomerular filtration rate decline in diabetic patients, according to data from many trials. There are, however, few investigations on the renoprotective effect of PTX medication, which delays the development of CKD to ESRD and dialysis in both diabetic and non-diabetic patients. The results of several clinical trials that highlight the renoprotective effect of PTX in individuals with chronic kidney disease are compiled in this paper.

KEYWORDS

Pentoxifylline(PTX), Proteinuria, ACEI/ARBS, Chronic Kidney Disease, Renoprotection, End stage renal disease

INTRODUCTION:

Globally, diabetes mellitus (DM) is one of the most significant health issues. Currently, about 450 million individuals suffer from diabetes mellitus (DM), and estimates suggest that by 2045, around 690 million people will have this disease.

Target organ problems resulting from diabetes mellitus, particularly micro- and macrovascular complications, will therefore rank among the most significant medical issues in the near future. [1] One important consequence of diabetes mellitus (DM) is diabetic kidney disease (DKD), which is the leading cause of end-stage renal disease (ESRD) in the western world. [2]

Proteinuria or albuminuria is a stand-alone risk factor that indicates the advancement of renal disease.[3]The most significant risk factor for the development of end-stage renal disease, according to extensive research including a large number of diabetes patients, was shown to be the urine protein excretion rate.[4] It is necessary to lower proteinuria in these individuals because of the elevated risk.[5] Information on the protective effects of angiotensin inhibitors has been documented in patients with type II diabetic nephropathy, despite the fact that acceptable and effective therapy is not fully recognised in these individuals. [6]

It has long been known that blood pressure may be changed to reduce the risk of renal disease developing further. It has recently been demonstrated that proteinuria is a separate predictor of the advancement of renal disease. A decrease in proteinuria throughout treatment is linked to a slower rate of progression, while a greater quantity of urine protein at the start of therapy is linked to a quicker rate of development. [7][8][9][10]

Urine protein excretion is linked to decreasing blood pressure, and angiotensin-converting enzyme (ACE) inhibitors are superior to other antihypertensive medications in this regard, both in terms of lowering urine protein excretion and delaying the advancement of renal disease. [11][12] To obtain other pharmacological activity besides RAS blockage, more study is required.[13] There is a dearth of medications for kidney diseases, and none that specifically target the advancement of renal disease have been brought to market. PDE, a cyclic nucleotide, has been employed in the recent past to target the advancement of chronic kidney disease. [14][15][16]

Thus, there is still work to be done in finding complementary or alternative strategies to maximize reno-protection. Using its capacity to lower blood viscosity and increase red blood cell deformability, pentoxifylline (PTX), a non-specific phosphodiesterase inhibitor, has been given to patients with occlusive peripheral vascular disorders for decades. [17] In addition to these hemorrhagic characteristics, PTX also has positive impacts on a number of other processes, including cell proliferation, inflammation, and the build-up of extracellular matrix, that are well-known to contribute to the advancement of chronic kidney disease. [18]

Efficacy Of Ptx On Non-diabetic Proteinuria

Clinical investigations in individuals with non-diabetic renal disorders, such as membranous glomerulonephritis and lupus nephritis, have demonstrated that PTX can reduce proteinuria in these conditions, in line with the findings on diabetic nephropathy. Table 1 provides an overview of clinical trials showing PTX's antiproteinuric efficacy in individuals with non-diabetic renal disorders.

Table 1 Efficacy of PTX in Non Diabetic Proteinuria

Investigators, years	Patients, number	Subjects	PTX dose	Control group	Follow up	Main outcome findings
Chen et al(2006) (19)	17	Non-diabetic patients with primary glomerular disease and persistent proteinuria	800 mg daily	-	6 months	Urinary protein excretion reduced significantly
Renke et al(2010) (20)	22	Non-diabetic patients with proteinuria	1200 mg daily + ACEI or ARB	Placebo + ACEI or ARB	8 weeks	Proteinuria reduced

Lin et al(2008) (21)	85	Patients with CKD and proteinuria	400-800 mg daily	Untreated control group	12 months	400-800 mg daily Untreated control group 12 months Proteinuria
Perkins et al(2009) (22)	40	Patients with CKD	800 mg daily	Placebo	1 year	Slower decrease in GFR, Proteinuria was not different between group.
ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CKD: Chronic kidney disease; GFR: Glomerular filtration rate.						

Chen et al. [19] found that therapy with PTX at a dosage of 800 mg daily for 6 months lowered proteinuria from average 2.82 to 1.79 g/g Creatinine (g/gCr) in 17 primary glomerulonephritic patients. The effectiveness was linked to a decrease in the excretion of urine monocyte chemoattractant protein (MCP)-1, suggesting a potential mechanism of action for PTX in individuals with proteinuria who are not diabetic. Then, in 22 non-diabetic individuals with proteinuria between 0.4 and 4.3 g/day and eGFR >30 mL/min/1.73 m2, Renke et al. [20] discovered PTX at a dosage of 1200 mg daily decreased proteinuria by 26% in comparison with placebo. This study was a placebo-controlled cross-over trial. Urinary N-acetyl-beta-d-glucosaminidase, α1-microglobulin, and C-reactive protein (CRP) did not alter across crossover periods.

In a randomized controlled trial, PTX's extra impact on proteinuria and GFR was assessed in 85 CKD patients who were previously on losartan, an ARB. PTX reduced proteinuria in patients with CKD stages 3 to 5 when added to losartan medication for a year, but there was no discernible improvement in GFR.[21] However, in a placebo-controlled research conducted by Perkins et al. [22], the effectiveness of PTF (400 mg twice daily) in slowing the decline in GFR and reducing proteinuria in 40 patients with chronic renal disease was assessed. The results showed diverse outcomes.

Proteinuria did not differ between the PTF and placebo groups at baseline, six months, or a year, but for PTF-treated participants, the mean estimated GFR decrease during treatment was slower compared with the year prior to study enrollment. The authors came to the conclusion that PTF could slow down high-risk patients' estimated GFR decline, possibly even without having any antiproteinuric effects.[22]

There was conflicting interpretation about the effectiveness of PTX on non-diabetic patients with proteinuria, nevertheless, because all of these trials were constrained by small sample sizes, brief observation periods, and biased designs.

Efficacy Of Ptx On Diabetic Proteinuria

Diabetes is becoming more common, and associated complications—primarily diabetic kidney disease—are becoming alarmingly more common. There is evidence to show that proinflammatory cytokines may have a pathogenic role in increasing glomerular permeability to albumin, which is a feature of diabetic nephropathy. Nowadays, improved glucose management and RAAS control are key components of diabetic nephropathy therapy. [23][24]

Peripheral vascular disease-related intermittent claudication is clinically treated with PTX [25]. Because it lowers blood viscosity, aggregation of platelets, erythrocyte stiffness, and erythrocyte aggregation, this medication has hemorheological effects. An increase in red blood cell deformability and flexibility results in an improvement in blood flow [26][27].

This characteristic, together with its ability to lower intraglomerular pressure, sparked early interest in PTX as a kidney disease treatment agent [28][29]. As an antiproteinuric, PTX is really supported by data from animal models and clinical trials. It's interesting to note that this antiproteinuric characteristic and its anti-inflammatory action, which was recently reported, are connected.[30][31][32][33][34][35][36]

By suppressing gene transcription and preventing mRNA accumulation, PTX can regulate TNFα levels [30][37]. Similar to this, it possesses a significant ability to regulate other pro-inflammatory cytokines, such as IL1, IL6, interferon γ [38][39][40], and other molecules such as VCAM1, ICAM1, and reactive C protein (CRP)[41][42]. Proteinuria may decrease as a result of PTX's anti-inflammatory action since DKD is a proinflammatory condition [43] with enhanced glomerular permeability to proteins [44]. Consequently, PTX may offer a potential therapeutic approach for DKD therapy.

Table 2 shows several clinical trials assessing PTX in renal patients have been carried out to date, the majority of whom are diabetic participants.

Investigators, years	Study design	Type of Intervention	Patients	PTX Dose	Main Findings
Aminorroaya et al., 2005 (45)	Randomized, controlled, open-label trial.	PTX vs. Captopril	DM patients, n = 39 Albuminuria > 300 mg/24 h; eGFR > 60 mL/min	1200 mg/day, 8 weeks	PTX and Captopril reduced proteinuria; 40% in PTX-group ($p < 0.05$) and 38.5% in Captopril-group ($p < 0.01$)
Rodriguez-Morán et al., 2005 (46)	Randomized, controlled, open-label trial.	PTX vs. Captopril	DM patients, n = 130 UAE 20–200 μg/min.	1200 mg/day, 6 months	PTX and Captopril reduced proteinuria; 77.2% in PTX-group and 76.6 % in Captopril-group ($p < 0.01$ for both)
Navarro et al., 2005 (47)	Randomized, controlled, open-label trial.	PTX vs. untreated	DM patients, n = 61 Albuminuria > 300 mg/24 h; eGFR > 90 mL/min	1200 mg/day, 4 months.	12.1% proteinuria reduction in PTX-group ($p < 0.001$)
Rodriguez-Morán et al., 2006 (48)	Randomized, double-blind controlled trial.	PTX vs. placebo	DM patients, n = 40 UAE 20–200 μg/min.	1200 mg/day, 4 months.	73.8% and 84.6% reductions in urinary levels of both high and low molecular weight proteins ($p < 0.05$)
Diskin et al., 2007 (49)	Open-label, controlled trial	PTX vs. untreated	Diabetic glomerulosclerosis patients, n = 14 Proteinuria > 1.5 g/24 h; Cr clearance > 15 mL/min	400–800 mg/day, 1 year	PTX not reduced proteinuria or improved renal function
Badri et al., 2013 (50)	Randomized, double-blind, controlled trial	PTX vs. placebo	Patients with GN, n = 18 proteinuria > 500 mg/24 h, mean eGFR 71.2 ± 30.6 mL/min/1.73 m2	800–1200 mg/day, 6 months	56% reduction of proteinuria without affecting GFR
Perkins et al., 2009 (51)	Randomized, double-blind, controlled trial	PTX vs. placebo	CKD patients, n = 40 mean eGFR 29.5 ± 10.1 mL/min/1.73 m2, proteinuria greater than 1 g/24 h	800 mg/day, 1 year	PTX stabilized GFR. No reduction of proteinuria
Goicoechea et al., 2012 (52)	Randomized, controlled trial	PTX vs. untreated	CKD patients, n = 91 albuminuria > 300 mg/24 h, eGFR <60 mL/min/1.73 m2	800 mg/day, 1 year	PTX stabilized GFR. No reduction of proteinuria

First, in non-hypertensive individuals with type 2 diabetes, Aminorroaya et al. [45] and Rodríguez-Morán et al. [46] found that PTX at a dosage of 400 mg three times daily showed anti-proteinuric effects similar to those attained using captopril 25 mg thrice daily. These investigations show that PTX has an anti-proteinuric effect that is comparable to that of ACEI, indicating a potential role for PTX in the treatment of diabetic proteinuria. Then, add-on PTX at a dosage of 1200 mg daily to background ARB for 4 months additively reduced proteinuria in patients with type 2 diabetes, according to Navarro et al. [47] in a randomised, open-label experiment.

Decreased levels of TNF-α in the urine and serum were linked to PTX's additional anti-proteinuric action. But the only relationship found between the change in albuminuria and the change in urine TNF-α was statistical. While this was going on, PTX at a dosage of 1200 mg daily for 4 months decreased both high (glomerular) and low (tubular) molecular weight urine protein excretion in normotensive type 2 diabetes patients with microalbuminuria in another experiment that used a double-blind, placebo-controlled design. [48]

PTX's possible renoprotective impact was assessed after the fact in a number of clinical investigations, some of which also looked at the medication's anti-inflammatory properties. However, the range of research designs, medication doses, and follow-up times used in these trials leads to outcomes that are not entirely definitive. After a year of follow-up, Diskin et al.'s [49] open-label, controlled study from 2007 that included diabetic patients with nephrotic proteinuria did not identify any further anti-proteinuric or renoprotective benefits of PTX medication in the context of ACEI and ARB therapy.

Unfortunately, the non-randomised design of this trial with just 14 individuals and the use of dual RAAS blockage have raised serious safety concerns. [53][54][55] In another randomised clinical study, proteinuria was reduced in the PTX group without changing eGFR.

This experiment was reported by Badri et al. in 2013 [50] and involved add-on PTX medication to baseline RAAS blocking in a small sample of non-diabetic individuals. Perkins et al. [51] noticed in 2009, in contrast to these findings, a reduction in the decrease of renal function in 40 diabetic patients with chronic kidney disease (CKD) stages 3 and 4 following a year of adding PTX to RAAS blocking.

Nevertheless, the authors suggested that this criterion may not necessarily represent the best surrogate result in these investigations because they did not see a decline in proteinuria levels. In patients with stage 3 or higher of chronic kidney disease (CKD), Goicoechea et al. [52] reported in 2012 that renal function had stabilized and numerous inflammatory markers (TNFα, fibrinogen, and high sensitivity CRP) were decreased. It should be highlighted that although PTX medication did not lower proteinuria in this group, a significant portion of patients dropped out and did not finish their follow-up.

Possible Mechanisms Underlying Ptx's Renal Effects

The most plausible reason for PTX's antiproteinuric activity in DKD patients is its ability to decrease the production of proinflammatory cytokines, according to a 2008 meta-analysis[56]. Tian et al.'s subsequent meta-analysis [57] found that, in DKD patients receiving RAAS blocking, PTX treatment was also able to additively decrease proteinuria and urine TNFα. Crucially, there are no alterations in hemodynamic or metabolism associated with this antiproteinuric effect [58].

Phosphodiesterase (PDEs) are inhibited by the medication PTX, among other consequences. By regulating the breakdown of cyclic adenosine-3,5-monophosphate (cAMP) as a feedback mechanism to return to basal levels, PDE activity affects intracellular second messenger cyclic nucleotides levels in mammalian cells [59][60]. By blocking PDEs, PTX keeps cAMP from being inactivated, which raises cAMP levels and activates protein kinase A (PKA) [59]. This lowers the production of pro-inflammatory cytokines such IL1, IL6, and TNFα.[60][61]

Most of the studies shows the renoprotective effect of PTX in CKD patients stage 1-4 . however its effect on patients with ESRD was inadequate . Chen et al [60] comes up with single-center observational study in 609 patients with CKD stage 3B to 5 before ESRD noted that add on PTX shows renoprotection in patient who have proteinuria as high as (≥1 g/gCr).hence proteinuria is the therapeutic marker for PTX.

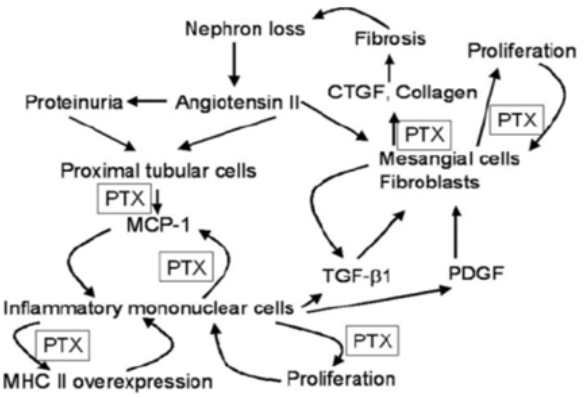

Figure 1: The renoprotective mechanisms of pentoxifylline in the treatment of chronic kidney disease. → indicates stimulation, secretion, or expression; PTX indicates that the pathway is inhibited by pentoxifylline. CTGF = connective tissue growth factor MCP-1 = monocyte chemoattractant protein-1; MHC = major histo compatibility complex; PDGF = platelet-derived growth factor; TGF-β1 = transforming growth factor-β1

In another high powered study Wu et al[61] noted that a total populations of 23,233 individuals diagnosed as advanced CKD with a serum Cr > 6 mg/dL and non dialysis patients during 6 months before and 3 months after the first prescription of erythropoietin stimulating agent, the patients who received PTX doesn't progress to ESRD . on the other hand patients who received ARB monotherapy doesn't show any protection from ESRD. This highlights the PTX 200MG was enough to suppress the risk of new onset ESRD.

Correspondingly, Kuo et al. [62] evaluated same data set and concluded that PTX along with RAS blockade halts the progression of advance CKD to ESRD and long term dialysis. hence it is appropriate to say that PTX reduces the risk of ESRD even in patients with late stage CKD.However all studies doesn't show concomitant anti-proteinuric and renoprotective effects by adding PTX to RAS blockade.

Perkins et al. [63] In a double- blind, randomized, placebo-controlled design, evaluated that there was less decline in eGFR in 40 patients (61% being diabetic) with CKD stages 3 to 4 exhibiting proteinuria >1 g/day who relieved PTX for about a year . and there the rate of decrease in eGFR was much slower than the previous enrollment. In contrast the authors did not noted PTX decline in proteinuria in comparison with the control group.Also there is inconsistent that PTX shows a greater action on tubulointerstitial injury than on glomerular filtration, proteinuria may or may not be surrogate outcome in demonstrating the effect of PTX on kidney function.

In another study which consists of greater percentage of African Americans and patients with diabetes in the PTX group, and displayed an unusually high rates of hospitalization (28–32%) and dropped-out (17.5%), reported by Goicoechea et al. [64] in open-label, randomized controlled trial, identified that in 91 patients with CKD stage 3 or higher who received 800 mg daily for 1 year shows reduction in inflammatory markers (TNF-α, fibrinogen and high sensitivity CRP) unjustified the anti proteinuric effect of PTX due to high drop out rate and insufficient follow up.

According to Diskin et al. [65] the small and non- randomized consisting of 14 adult-onset, insulin-dependent diabetic patients with nephrotic proteinuria and creatinine levels as high as (>11 mL/min per year) doesn't show effective anti proteinuric effect of PTX at a dose of 400–800 mg [66,][67].

CONCLUSION:

In conclusion, a promising direction in the study of nephrology is the use of pentoxifylline in the treatment of proteinuria. With its diverse pharmacological characteristics, pentoxifylline may help treat proteinuria, especially in individuals with different types of renal diseases, according to the growing body of research.

Research has indicated that pentoxifylline possesses anti-inflammatory, anti-fibrotic, and vasodilatory characteristics, all of which may be responsible for its possible renoprotective qualities.

Pentoxifylline may help attenuate proteinuria and preserve renal function by focusing on underlying mechanisms that are implicated in renal damage, such as the decrease of oxidative stress and the regulation of cytokine production.

Moreover, pentoxifylline's safety and tolerability characteristics make it a desirable choice for proteinuria treatment regimens. The fact that it has been used successfully to treat other illnesses including peripheral vascular disease increases the confidence that it is safe to use in clinical settings. Notwithstanding the encouraging results, it is imperative to recognise the necessity for more investigation, including meticulously planned clinical studies, to clarify the ideal dosage schedules, patient eligibility standards, and enduring effectiveness of pentoxifylline in the treatment of proteinuria. Furthermore, given the variability of renal disorders, future research ought to focus on particular subgroups that would gain the most from pentoxifylline treatment.

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