THE EFFECT OF PENTOXIFYLLINE ON EGFR AND PROTEINURIA IN DIABETIC PATIENTS WITH CHRONIC KIDNEY DISEASE: A CASE-CONTROL STUDY

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Abstract:

Background: Chronic kidney disease (CKD) is an important worldwide health problem. Multidrug interventions with the least adverse effects should be investigated in attempts to stop CKD progression. This study aims to evaluate the effect of pentoxifylline (PTF) on CKD progression regarding serum creatinine, estimated glomerular filtration rate (eGFR), urinary Albumin/creatinine (A/C) ratio and blood hemoglobin level. This study included 53 patients with CKD stages 3-4, stable clinical condition and stable renal function were randomly assigned to continue with their standard treatment (control group: 23 patients) or to treatment with oral pentoxifylline (pentoxifylline group: 30 patients), at 400 mg twice a day to be reduced to 400 mg once daily in patients with severe renal dysfunction (Creatinine clearance < 50ml/min) for six months. Serum creatinine, eGFR (by the Modification of Diet in Renal Disease (MDRD) study equation) and urinary protein excretion will be monthly monitored for 6 months and picked-up at the end of the study. **Results:** The proteinuria rise were found to be significantly lower ($p<0.001$), and the hemoglobin rise was found to be significantly higher ($p=0.002$) in the pentoxifylline group, compared to the controls. However, eGFR decline and initiation of hemodialysis showed statistically insignificant differences between the pentoxifylline group and the control group, (p=0.249 and 0.436). Correlation analysis demonstrated that eGFR change was found to have a significant weak positive correlation with hemoglobin change ($r=0.307$, p=0.030) in the pentoxifylline group. Also, eGFR decline and hemodialysis initiation were found to be significantly higher in congestive heart failure (CHF) than non-CHF patients ($p=0.003$ *and* $p=0.009$) in the control group. **Conclusion:** Pentoxifylline was found to significantly decrease proteinuria rise and improve anemia. However, it has insignificant effect in delaying eGFR decline in patients with CKD stages 3 to 4

Keywords: pentoxifylline; chronic kidney disease; creatinine; eGFR; A/C ratio; proteinuria; hemoglobin; anemia; hemodialysis.

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1. Background:

Chronic kidney disease (CKD) is an important worldwide health problem.[1] Diabetic kidney disease (DKD) is the most frequent cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in the USA.[2] Current interventions with proven efficacy, such as glycemic and blood pressure control, dietary protein restriction, and angiotensin II blockade, slow the progression of chronic kidney disease (CKD); however, long-term cessation of CKD progression remains unclear. Because of the pathogenetic complexity of this condition, multidrug interventions with the least adverse effects should be investigated as the next step in attempts to stop CKD progression.[3]

The non-specific phosphodiesterase inhibitor pentoxifylline (PTX) was approved by the US Food and Drug Administration (FDA) in 1984 for the treatment of peripheral vascular disease (PVD). PTX has been shown in several animal models of kidney disease to reduce proteinuria and preserve renal function. These effects are associated with a reduction in inflammation, oxidative stress and fibrosis. [4]

PTF shows anti-inflammatory, anti-proliferative, and anti-fibrotic properties, which attenuate renal disease progression in animal models. [5]

PTF inhibit production of pro-inflammatory cytokines, such as monocyte chemotactic protein -1 (MCP-1), interleukin -1 (IL-1), IL-6, and tumor necrosis factor-alpha (TNF-α). A change in urinary TNF-α levels was correlated directly with changes in urinary albumin excretion and inversely correlated with changes in eGFR. [6] Pentoxifylline can suppress activation and proliferation of

mesangial cells, lymphocytes, and renal fibroblasts, all of which play important roles in renal fibrosis. [7]

Notably, pentoxifylline is a safe drug that is usually well tolerated when administered as the conventional controlled-release formulation: gastrointestinal symptoms (i.e. nausea and dyspepsia) and dizziness are the most common complaints and affect about 3% of patients. [3] Although accumulation of the active metabolite of pentoxifylline has been documented in moderate and severe renal dysfunction during multidose pharmacokinetic studies, the clinical significance of this is unclear. Dosage reductions to 400 mg twice daily in patients with moderate renal dysfunction, and to 400 mg once daily in patients with severe renal dysfunction, are recommended. [8]

Therefore, our aim is to evaluate the effect of pentoxifylline on eGFR and proteinuria in diabetic patients with chronic kidney disease stages 3-4 without renal replacement therapy compared to values in controls continued with their standard treatment.

2. Subjects and methods

Over a period of twenty-two months (starting from March, 2021 till December, 2022, we studied 53 patients with CKD stages 3-4, stable clinical condition (defined as no hospitalizations or cardiovascular events within the 3 months before screening) and stable renal function (baseline serum creatinine has to have not increased by 50% in the 3 months before screening) randomly assigned to continue with their standard treatment (control group: 23 patients) or to treatment with oral pentoxifylline (pentoxifylline group: 30 patients), at 400 mg twice a day to be reduced to 400 mg once daily in patients with severe renal dysfunction (Creatinine clearance < 50ml/min) for six months. The dosage of antihypertensive drugs, anti-diabetic medications, lipid-lowering agents, and anti-platelet drugs was continued with adjustment according to the individual patient's clinical condition. All subjects were collected from the nephrology outpatient clinic of the Internal Medicine department in Kasr Alainy hospital of Cairo university. All participants are between 18 and 65 years old.

2.1. Study design: interventional case-control study

2.2. Exclusion Criteria:

1. Patients with a history of PTF hypersensitivity.
2. Patients already on PTF treatment.
3. Patients with active infections, inflammatory diseases, human immunodeficiency virus (HIV) infection and those with chronic liver disease.
4. Patients who had received immunosuppressive therapy.

The Medical Research Ethics Committee at Kasr Al Ainy School of Medicine, Cairo University, Cairo, Egypt, gave its approval to the study plan under number (MD-102-2021).

All participants gave their permission in writing after being fully informed.

All participants underwent thorough clinical evaluation including history taking process that included questions about age, chronic illness, cause and duration of CKD and drug use history.

2.3. Laboratory tests: serum creatinine and urinary albumin/creatinine ratio were measured at the start of the study, monthly monitored for 6 months and picked-up at the end of the study. Estimated glomerular filtration rate (eGFR) level calculation (ml/min/1.73 m^2) using the formula of the MDRD study equation.

2.4. Statistical analysis:

The collected data were coded and entered using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum and maximum for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using unpaired t test in normally distributed quantitative variables while non-parametric Mann-Whitney test was used for non-normally distributed quantitative variables [9] . For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5.[10]Correlations between quantitative variables were done using Spearman correlation coefficient.[11] P-values less than 0.05 were considered as statistically significant. Data will be presented as Mean and Standard deviation(± SD) for quantitative parametric data, and Median and Interquartile range for quantitative non parametric data. Frequency and percentage will be used for presenting qualitative data .

3. Results

Baseline characteristics of the cases included in the present study are listed in Table (1). The data didn't show statistically significant differences between the two groups.

The A/C ratio rise (*p=0.045)* were found to be significantly lower in the PTF group, compared to the controls, (figure 1). However, creatinine rise, (*p=0.297*) and eGFR decline, (*p=0.567*) showed statistically insignificant differences between the PTF group and the control group,Table (2).

No statistically significant differences in A/C ratio change and eGFR change between patients who were receiving renin angiotensin aldosterone sysytem (RAAS) blockade drugs and non users among each group, Tables (3 and 4) .

No significant correlations were found between AC ratio change, creatinine change and eGFR change and other studied parameters.

No statistically significant differences in A/C ratio change and eGFR change regarding age, gender, duration of CKD or the presence of dyslipidemia, ischemic heart disease (IHD), cardiovascular disease (CVD or peripheral vascular disease (PVD) between patients among each group.

Table 1. Demographic, clinical and laboratory data of the 53 participants of our study.

			control group	PTF group	P value
Age	**Years**	**Mean ±SD**	51.565±9.6945	49.033 ±10.1386	0.363
Gender (M/F)		**M/F**	11/12	17/13	0.523
baseline creatinine	**mg/dl**	**Mean ±SD**	2.565±0.8127	2.680±0.6754	0.577
Baseline eGFR	**ml/min/1.73m^2**	**Mean ±SD**	25.43±8.56	25.02±10.49	0.879
CKD stage	**3A**	**(*n*, %)**	1 (4.3%)	3 (10%)	0.256
	3B	**(*n*, %)**	6 (26.1%)	3 (10%)	
	4	**(*n*, %)**	16 (69.6%)	24 (80%)	
Duration	**Years**	**Mean ±SD**	3.0870 ±1.18372	2.5750±1.42052	0.169
baseline A/C ratio	**mg/g**	**Mean ±SD**	762.217±574.2085	611.767±657.1052	0.387
Hypertensive		**(*n*, %)**	15 (65.2%)	23 (76.7%)	0.359
Dyslipidemic		**(*n*, %)**	14 (60.9%)	12 (40%)	0.123
Ischemic Heart		**(*n*, %)**	10 (43.5%)	7 (23.3%)	0.119
CHF		**(*n*, %)**	5 (21.7%)	6 (20%)	0.877
CVD		**(*n*, %)**	1 (4.3%)	4 (13.3%)	0.267
PVD		**(*n*, %)**	19 (82.6%)	24 (80%)	0.810
RAAS blockade		**(*n*, %)**	5 (21.7%)	11 (36.7%)	0.241

Table 2. Creatinine change, eGFR change, A/C ratio change and initiation of hemodialysis in study population.

	Control		**PTF**		**P value**
	Mean	**SD**	**Mean**	**SD**	
creatinine change (mg/dl)	0.6	0.97980	0.3400	0.81605	0.297
eGFR change (ml/min/1.73m^2)	-3.0836	3.00114	-2.3294	5.69291	0.567
AC change (mg/g)	118.2174	118.2174	0.1333	185.77178	0.045
Hemodialysis (n,%)	0	0%	0	0%	

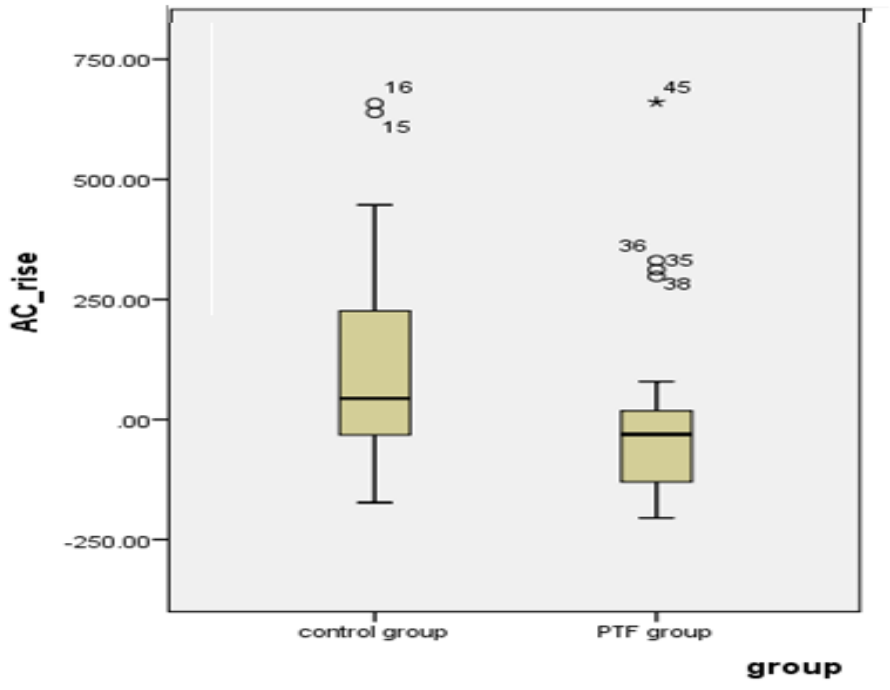

Fig.1 A/C ratio change of study population.

Follow up of 53 diabetic patients with CKD patients stage 3-4 revealed a significantly lower A/C ratio change in the PTF group, compared to the controls.

Table 3 Comparison between RAAS blockade drug users and non-users regarding creatinine change, eGFR change and A/C ratio change in the control group.

Control			
	RAAS block	**Non- RAAS block**	**P value**
	Mean±SD	**Mean±SD**	
creatinine change (mg/dl)	0.2200±0.38341	0.7056±1.07401	0.667
eGFR change (ml/min/1.73m^2)	-3.0477±3.75034	-3.0936±2.88895	0.584
A/C ratio change (mg/g)	232.6000±282.04131	86.4444±215.11945	0.344

Table 4 Comparison between RAAS blockade drug users and non-users reagarding creatinine change, eGFR change and A/C ratio change in the PTF group.

PTF			
	RAAS block	**Non- RAAS block**	**P value**
	Mean±SD	**Mean±SD**	
creatinine change (mg/dl)	0.3091±0.54121	0.3579±0.95354	0.314
eGFR change (ml/min/1.73m^2)	-4.0348±8.53392	-1.3421±2.99142	0.273
A/C ratio change(mg/g)	7.0000±167.88329	-3.8421±199.74380	0.536

4. Discussion

Chronic kidney disease (CKD) is an important worldwide health problem.[1] Diabetic kidney disease (DKD) is the most frequent cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in the USA.[2] Current interventions with proven efficacy, such as glycemic and blood pressure control, dietary protein restriction and angiotensin II blockade, slow the progression of chronic kidney disease; however, long-term cessation of CKD progression remains unclear. PTF shows anti-inflammatory, anti-proliferative, and anti-fibrotic properties, which attenuate renal disease progression in animal models. [5]

We aimed to evaluate the effect of pentoxifylline on eGFR and proteinuria in diabetic patients with chronic kidney disease stages 3-4 without renal replacement therapy compared to values in controls continued with their standard treatment.

In our study, the A/C ratio rise was found to be significantly lower in the PTF group, compared to the controls which agreed with Lin et al who reported 56 patients (72% being non-diabetic) with CKD stages 3 to 4 and urinary protein excretion >0.5 g/gCr in an open-label, randomized controlled trial. These patients had received angiotensin receptor blocker (ARB) (losartan 100 mg daily) for at least 6 months at entry, and were allocated to receive either ARB or add-on PTF (400 mg once or twice daily depending on eGFR levels) to ARB. It was concluded that the add-on PTF group displayed a lower proteinuria than the ARB group after 1 year. [12] Navarro-González et al reported the PREDIAN trial, the largest open-label, randomized controlled study to date, which comprised 169 type 2 diabetics at CKD stages 3 to 4 with albuminuria>30 mg/day under maximal rennin angiotensin system blockade. After 24 months of treatment, a higher reduction of albuminuria and a lower decrease in the eGFR were observed in the PTF group. [13]

McCormick et al reviewed 10 studies including a total of 476 participants (adult patients with diabetic kidney disease who received oral pentoxifylline) with a median duration of 6 months and found pentoxifylline significantly decreased proteinuria compared with placebo or usual care. But when compared with captopril, the decrease in proteinuria with pentoxifylline was similar. [14]

The anti-proteinuric and renoprotective effects of PTF in CKD may arise from its ability to inhibit production of pro-inflammatory cytokines, such as MCP-1, IL-1, IL-6, and TNF-α .[15-17]

In contrary to Perkins et al who examined add-on PTF (800 mg daily) to RAS blockade in 40 patients with CKD stages 3 to 4 exhibiting proteinuria>1 g/day and did not observe PTF decreased proteinuria in comparison with the control group after 1 year. [18]

Also, Diskin et al reported 14 adult-onset, insulin-dependent diabetic patients with nephrotic proteinuria in an open-label, controlled trial. At 1 year, the authors did not find additive anti-proteinuric or renoprotective effects of PTF at a dose of 400–800 mg daily on background angiotensin converting enzyme inhibitors (ACEIs) plus ARBs. [19]

It may be due to the renoprotective effect of RAS blockade, it may be hard to observe extra benefits of PTF on top of RAAS blockade, especially in studies with short treatment duration.

In our study, creatinine rise and eGFR decline and initiation of hemodialysis showed statistically

insignificant differences between the PTF group and the control group which agreed with McCormick et al who found no significant changes in systolic or diastolic blood pressure or glomerular filtration rate. [14]

This also agreed with Lin et al who revealed a significant decrease of eGFR in the ARB but not the add-on PTF group at 12 months. [12]

Mechanistically, add-on PTF therapy reduced changes in urinary TNF-α and MCP-1 as compared to the ARB group. In fact, due to the potent renoprotective effect of RAAS blockade, and the insidious nature of renal progression, it may be hard to observe extra benefits of PTF on top of RAAS blockade, especially in studies with short treatment duration.

This can be explained as most published literatures were limited by small sample size, short observation period and imperfect methodology using surrogate outcomes (proteinuria, eGFR decline). There is need for more well-designed studies with longer duration of follow-up aiming at hard renal endpoints (end stage renal disease, doubling of serum creatinine). Also PTF is an old drug that lacks financial sponsorship.

In contrary to de Morales et al who conducted their study on 91 participants (46 in the pentoxifylline group (400 mg/twice a day) and 45 in the control group) followed up for 7 additional years and found that renal event was recorded in 24 patients from control group (13 initiated dialysis therapy and serum creatinine doubled in 11) and 11 patients from PTF group (7 initiated dialysis and serum creatinine doubled in 4). [20]

This also disagreed with Chen et al who conducted a retrospective study of 661 patients with an eGFR<45 ml/minute/1.73 m2 . A total of 419 patients used PTF and ACEIs or ARBs, and 242 patients used ACEIs or ARBs only. The participants were followed a median follow-up period of 2.25 years. Patients using PTF had a better renal outcome compared with patients without PTF use. [21]

Also, Kuo et al conducted a prospective cohort study to evaluate the effect of PTF plus ACEIs vs ACEIs/ARBs alone in patients with CKD stage 5 who had not yet received dialysis. They reported that after propensity score-matching, use of PTF was associated with a lower-term dialysis or death in ACEI/ARB users or ARB users. [22]

Perkins et al. found the mean eGFR decrease was significantly less in the PTF group than the placebo group. [18]

The conclusions of those studies were limited by several factors, including the analysis of kidney function as a secondary objective, the inadequate sample size, the heterogeneity of primary renal disease, and incomplete follow-that up. Other studies reported PTF treatment stopped the decrease in eGFR independently of its antiproteinuric properties, suggesting additional protective effects on kidney function. [18]

Our study was limited by several factors:

1. It was not a double blind trial.
2. The relative small number of the patients studied which may decrease
   the statistical power and reproducibility of results.
3. The observation period is too short for robust conclusions to be drawn.
4. The data are from a single center.
5. Despite the possible beneficial results of treatment with PTF in CKD patients in the previous Randomized clinical trials, participants were not required to adhere to randomly assigned treatment during the long-term follow-up and crossovers may bias toward the null.

We could thus recommend evaluating the effect of pentoxifylline on diabetic patients with CKD in double blind multicenter large cohort studies with long observation period.

5. Conclusion

In this study, we evaluated the effect of pentoxifylline on CKD progression regarding serum creatinine, eGFR, urinary albumin/creatinine ratio in diabetic patients with chronic kidney disease stages 3-4 without renal replacement therapy compared to values in controls continued with their standard treatment.

We discovered that The A/C ratio rise was significantly lower, and the hemoglobin rise was significantly higher in the PTF group, compared to the controls. This could be explained by its ability to inhibit production of pro-inflammatory cytokines, such as MCP-1, IL-1, IL-6, and TNF-α .[15-17] These make pentoxifylline a promising drug in preventing the progression of proteinuria in diabetic patients with CKD.

We didn't find any significant differences between control group and PTF group regarding creatinine change, eGFR change, hemodialysis initiation.

Ethics approval and consent to participate The study protocol was approved by the Medical Research Ethics Committee at Kasr Al Ainy School of Medicine, Cairo University, Cairo, Egypt, under number (MD-102-2021). Written informed consent was obtained from all participants.

Consent for publication The consents of publication are available from the corresponding author on reasonable request

Availability of data and materials The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests The authors declare that they have no competing interests.

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Author contributions KMS and TSA: conceptualized the study. KMS, AD and NMS: supervision, design, reviewing, and editing and final approval of the version to be submitted for publication; ME: data collections, data analysis and interpretation and writing the manuscript. The final version has been read, revised, and edited by all authors to be submitted for publication.

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Abbreviation

CKD Chronic kidney disease
PTF Pentoxifylline
eGFR Estimated glomerular filtration rate
A/C Albumin/creatinine
MDRD the Modification of Diet in Renal Disease
CHF Congestive heart failure
MCP Monocyte chemotactic protein
IL-1 Interleukin -1
TNF-α Tumor necrosis factor-alpha
HIV Human immunodeficiency virus
RAAS Renin angiotensin aldosterone sysytem
IHD Ischemic heart disease
CVD Cardiovascular disease
PVD Peripheral vascular disease
ARB Angiotensin receptor blocker
ACEI Angiotensin converting enzyme inhibitor

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