Effect of Pentoxifylline on Progression of Diabetic Nephropathy

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Abstract

Background: Pentoxifylline is nonspecic phosphodiesterase inhibitor used for treatment of peripheral vascular disease. This drug has some antiproteinuric effects and delay in the loss of estimated Glomerular Filtration Rate (GFR) in Diabetic Kidney Disease. To evaluate the effects of add-on pentoxifylline for reduction of albuminuria in patients with DKD.

Materials and methods: 50 Eligible participants were included having DN presented with Urinary Albumin (UA) excretion greater than 30 mg/gm and having stable renal function and randomly allocated to two groups. Each group had 25 patients. Experimental group received Pentoxifylline. Both groups received Losartan and other antihypertensive and antidiabetic medication as per need. Patient were evaluated clinically with (Blood Pressure) and biochemically with (S. creatimine, eGFR, uACR, fasting blood glucose, blood glucose 2 hrs after breakfast, HBA_1c and urinary TNF- α level) at baseline, at 3rd month and at 6th month for outcome evaluation.

Results: At the end of six month, uACR and urinary TNF-α decreased in the experimental group from 664±180 mg/gm and 11.72±3.73 ng/g to 567±181 and 8.85±3.57 respectively (p=<0.001). By contrast, uACR and TNF- α level did not change in the control group. Furthermore, the reduction of uACR was strongly correlated with the decrease of TNF- α (r=0.56, p=0.01) in the experimental group, but not in the control group. eGFR was stable in experimental group during 6 months but decreased significantly from baseline in control group (p=0.02). Treatment effect (NNT) in terms of reduction of proteinuria by >30% of baseline within 6 months was calculated and NNT was 13.

Conclusion: PTX can serve as adjuvant therapy for further reducing proteinuria which may delay the progression of DN.

Key words: DKD (Diabetic Kidney Disease); Diabetic Nephropathy (DN); Pentoxifyllie (PTX); Number Needed to Treat (NNT); Tumour Necrosis Factor-α (TNF- α); uACR (Urinary Albumin Creatinine Ratio).

Introduction

Diabetes Mellitus (DM) is the fourth leading cause of death after cancer, cerebrovascular disease, heart disease.[1] Prevalence of DM in Bangladesh increased from 4% in 1990 to 10% in 2011 and may reach 13% by 2030.[2,3]

Diabetic Nephropathy (DN) is characterized by proteinuria (Generally defined as urinary albumin excretion greater than 30 mg/24 hr) hypertension and advanced renal insufficiency. DN is a chronic microvascular complications of DM which is associated with significant morbidity and mortality and one of the main cause for end stage renal disease which increase renal replacement therapy.[4-6]

The understanding of the pathophysiologic processes leading to Diabetic Kidney Disease (DKD) has evolved tremendously in recent years. Nowadays, it is recognized that both the chronic low-grade in ammation and the activation of the innate immune system occurring in DM are related to diabetic complications, becoming key pathophysiological mechanisms involved in the development and progression of DKD. Plasma concentrations of inflammatory molecules, including pro-inflammatory cytokines, are elevated in patients with DM[7]. Pro-inflammatory cytokines can lead to the development of microvascular diabetic complications, including nephropathy.

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Submitted on : 14.05.2024
Accepted on : 10.07.2024

A potential relationship exist between the elevated levels of TNF-α and the development and progression of renal injury in DM.[8] This cytokine is cytotoxic to glomerular, mesangial and epithelial cells and may induce signi cant renal damage.[9] In DKD, urinary TNF-α has been suggested as a critical factor contributing to sodium retention and renal hypertrophy, important renal alterations that occur during the initial stage of this disease.[10] Moreover, it has been demonstrated that increased urinary as well as renal interstitial concentrations of TNF-α precede the rise in albuminuria.[11]

Pentoxifylline (PTX) (3,7-dimethyl-1-(5-oxohexyl)-3, 7-dihydro-1H-purine-2,6-dione) is a methyl-xanthine derivative that was approved by the United States Food and Drug Administration for the treatment of intermittent claudication more than 30 years ago (US FDA). The primary hemorheological effects of PTX are due to increased red blood cell deformability and decreased blood viscosity, although it affects almost all factors responsible for blood viscosity and can be considered as an almost complete rheological drug.[12] However, PTX also has important effects as a modulator of in ammation, which supports its use as a renoprotective drug in DKD.[13]

PTX is able to modulate TNF-α levels by inhibiting the gene transcription and blocking mRNA accumulation.[14] Likewise, it has a considerable capacity to modulate other pro-in ammatory cytokines, including IL1, IL6, interferon-γ and other molecules like the intercellular adhesion molecule 1, the vascular cell adhesion molecule 1, and the reactive C protein.[15,16] Since DKD is a proin ammatory state with increased glomerular permeability to proteins, the anti-in ammatory effect of PTX could result in a reduction of proteinuria.[17,18] Therefore, PTX might represent a novel therapeutic approximation to the treatment of DKD.

A meta-analysis published in 2008 pointed to the capacity of PTX to reduce the production of proin ammatory cytokines as the most likely explanation for its antiproteinuric action in patients with DKD.[19] A subsequent meta-analysis concluded that PTX therapy was also able to additively reduce proteinuria and urinary TNF-α in patients with DKD under RAAS blockade.[20] Most recently in another meta-analysis concluded that, PTX may constitute a further therapeutic intervention in DKD patients to background RAAS blockade.[21]

There is scarcity of study regarding the role of PTX in DN in our country. Therefore, in this study we speculated that PTX can serve as an adjuvant therapy for DN patients receiving standard treatment and further reduce proteinuria. Our study aimed to evaluate the efficacy of PTX as an adjuvant therapy for DN patients receiving standard treatment.

Materials and methods

This was a single-centered, open-labeled, quasi experimental study conducted in Department of Nephrology, Chittagong Medical College Hospital (CMCH) from June 2018 to May 2019 after approval Ethical review Committee, CMCH. 50 Eligible participants were included having DN presenting with Urinary Albumin (UA) excretion greater than 30 mg/gm and having stable renal function. Patients were randomly allocated to two groups, experimental and control group. Each group contained 25 patients. Experimental group received Pentoxifylline. Both groups received Losartan and also other antihypertensive and antidiabetic medication as per need. Patients were evaluated clinically (Blood Pressure) and biochemically (S. creatimine, eGFR, uACR, Fasting blood glucose, blood glucose 2 hrs after breakfast, HBA_1c and uriary TNF-α a level) at baseline, at 3rd month and at 6th month for outcome evaluation. All patients attending the OPD of Department of Nephrology and Endocrinology with a diagnosis of T2 DM were assessed for eligibility. Informed written consent was obtained from the patients or attendants after full explanation of the ultimate outcome, complications and purpose of the study. They were also informed to withdraw from the study at any stage.

Control group received Losartan and experimental received Losartan and Pentoxifylline according to eGFR for six months. Patient assigned to the treatment group started PTX according to eGFR : 400 mg twice daily for eGFR 59-30 ml/min/1.73m^2 and 400mg daily for eGFR

29-15ml/min/ 1.73m.^{2} Pentoxifylline was given in full stomach to avoid GI side effect. Eligible patients were followed up in every 3 months interval through history, physical parameter like BP, BMI and relevant investigation such as serum creatinine level, Urine R/E, Blood glucose-fasting and 2 hours after breakfast, HbA_1c, uACR. Urinary TNF alpha were measured at starting and after 6 month of drug therapy. After collection of data, all were entered into Microsoft Xcel data sheet and SPSS (Statistical Package for Social Science) for Windows version 23 software for the processing and analyses.

Results

Overall the median (IQR) age of the ourstudy participants were 53 (46-65) with male predominance (Male to female ratio was 1.5:1. However, both the groups were similar with respect to their age and sex distribution.

Majority of our patients in both the groups had HTN, had DM for >10 years and in CKD stage 3. Both the groups were comparable with respect to presence of HTN, duration of DM, stage of CKD, BMI, SBP and DBP at baseline.

Both groups did not differ for baseline glycemic status, serum creatinine, eGFR, urinary albumin excretion and urinary excretion of TNF-α.

Comparison of patients' systolic and diastolic blood pressure at studied time points. Patients' systolic and diastolic blood pressure at studied time points, in both Pentoxifylline and control groups, was not statistically significantly different (p value > 0.05).

Ccomparison of patients' blood sugar (Fasting and 2 hours post-parandial) and Hemoglobin A1c at studied time points. Patients' glycemic status with respect to these three parameters at studied time points, in both Pentoxifylline and control groups, was similar (p value > 0.05).

Table I Comparison of renal function between groups during study period

Parameters (Unit)	Time interval	Study Groups	n	(Mean ± SD)	p value
Serum creatinine (mg/dl)	Baseline	Pentoxifylline	25	1.92±0.64	0.45^{NS}
		Control	25	2.06±0.54	
	Month 3	Pentoxifylline	25	1.90±0.70	0.53 ^{NS}
		Control	25	2.07±0.53	
	Month 6	Pentoxifylline	25	1.90±0.64	0.48 ^{NS}
		Control	25	2.18±0.53	
eGFR (ml/min per 1.73 m^2)	Baseline	Pentoxifylline	25	36.65±10.91	0.38 ^{NS}
		Control	25	35.28±10.23	
	Month 3	Pentoxifylline	25	37.21±10.18	0.86^{NS}
		Control	25	34.01±10.54	
	Month 6	Pentoxifylline	25	38.43±11.98	0.52^{NS}
		Control	25	33.18±10.14	
uACR (mg/gm)	Baseline	Pentoxifylline	25	664±180	0.54 ^{NS}
		Control	25	623±229	
	Month 3	Pentoxifylline	25	619±196	0.99 ^{NS}
		Control	25	620±216	
	Month 6	Pentoxifylline	25	567±181	0.024^{S}
		Control	25	640±204	

p values were derived from independent sample t test, NS: Statistically Not Significant. S: Statistically significant.

Table I shows the comparison of patients' renal function (Serum creatinine, eGFR and uACR) at studied time points. Though, there was a trend of reduction of serum creatinine and increase of eGFR in Pentoxifylline group and opposite trends were observed in control group, these were not statistically significant (p value > 0.05). uACR was significantly lower at final 6 month follow-up than control group (p=0.024).

Table II Change of serum creatinine, eGFR and UACR from baseline to month 6 in Pentoxyphylline group

Variables (Unit)	Mean (±SD) values		Mean difference [95% CI]	p value
	At Baseline	At month 6		
Serum creatinine (mg/dl)	1.92±0.64	1.90±0.64	0.02 [0.00 to 1.08]	0.56^{NS}
eGFR (ml/min per 1.73 m^2)	36.65±10.91	38.43±11.98	1.56 [0.25 to 2.89]	0.08 ^{NS}
uACR (mg/gm)	664±180	567±181	96 [66 to 126]	<0.001^{S}

CI: Confidence Interval, p values are derived from paired sample t test, S: Statistically Significant, NS: Statistically Not Significant.

In the Pentoxifylline group there was a trend of reduction of serum creatinine and increase of eGFR during follow-up. But the difference from baseline to 6 month were not statistically significant p value > 0.05). However, uACR was significantly reduced from baseline to 6 month (p<0.001).

Table III Change of Serum creatinine, eGFR and UACR from baseline to month 6 in control group

Variables (Unit)	Mean (±SD) values At Baseline	At month 6	Mean difference [95% CI]	p value
Serum creatinine (mg/dl)	2.06±0.54	2.18±0.53	-0.12 [-0.00 to -0.93]	0.03 S
eGFR (ml/min per 1.73 m^2)	35.28±10.2	33.18±10.14	2.10 [0.31 to 3.93]	0.02 S
UACR (mg/gm)	623±229	640±204	-17 [-43 to 10.25]	0.21 NS

CI: Confidence Interval, p values are derived from paired sample t test, S: Statistically Significant, NS: Statistically Not Significant.

In the control group there was a trend of increase of serum creatinine and reduction of eGFR during follow-up and the difference from baseline to 6 month were statistically significant (p value <0.05). However, the change of uACR was not statistically significantly from baseline to 6 month (p=0.21).

Table IV Within group change of urinary TNF-α from baseline to month 6

Study group	Mean (±SD) value of urinary TNF-α (ng/g) At baseline	At month 6	p value
Pentoxifylline	11.72±3.73	8.85±3.57	<0.001 S
Control	9.87±3.84	10.18±3.86	0.06 NS

p values are derived from paired sample t test, S: Statistically Significant, NS: Statistically Not Significant.

In the experimental group urinary TNF-α reduced significantly from baseline to 6 months after treatment (Table IV). In the control group there was no significant change of TNF-α from baseline to 6 month follow up.

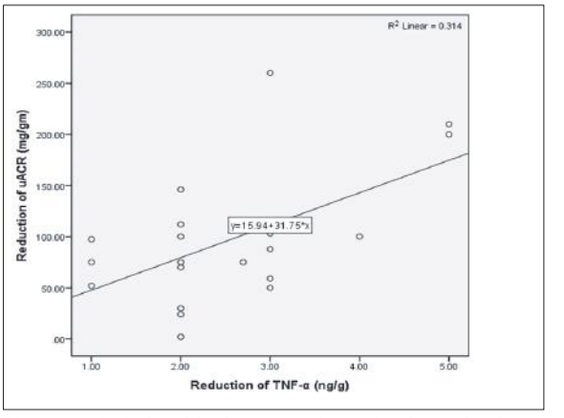

Figure 1 Relationship between the reduction of urinary albumin excretion and the decrease of urinary tumor necrosis factor-alpha concentrations in patients treated with Pentoxifylline

In patients treated with PTX, the reduction in urinary TNF-α concentration was directly correlated with the change in UACR (r=0.56, p=0.01) (Figure 1).

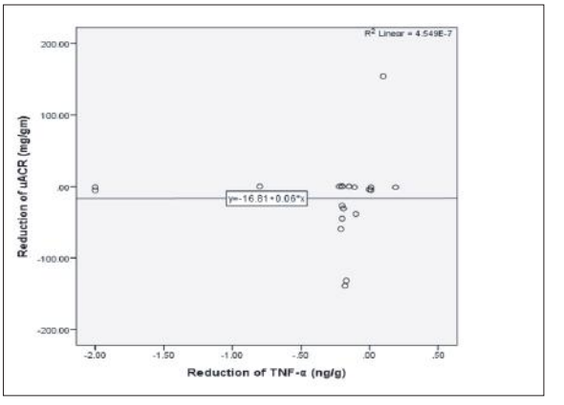

Figure 2 Relationship between the reduction of urinary albumin excretion and the decrease of urinary tumor necrosis factor-alpha concentrations in patients treated without Pentoxifylline

There was no significant correlation between changes in urine TNF-α with variations of UACR in the control group (r=0.027, p=0.91) (Figure 2).

Discussions

In our study in the experimental group the mean difference of uACR from baseline to 6 months after treatment was 96 mg/gm [95% CI: 66 to 126, p <0.001]. On the contrary, in the control group there was statistically insignificant increase of uACR 7mg/gm [95%CI: -43 to 10.25, p=0.21]. In a prospective and randomized study showed an

additional effect on the reduction of urinary albumin excretion of treatment with PTX in a group of patients with DKD and residual albuminuria despite long-term therapy with angiotensin II receptor blockers at the recommended dosage.[22] In a recent randomized trial in renal disease progression as a secondary objective and observed that mean eGFR signi cantly increased 2.5 ml/min per 1.73 m^2 after 12 months in the PTX group, compared with amean 5.2ml/minper 1.73 m2 reduction in the control group.[23] Most recently, in the PREDIAN trial, to date the largest RCT to evaluate the renoprotective effects of PTX. The study comprised 169 type 2 diabetic subjects with CKD stages 3 and 4 and residual albuminuria despite RAAS blockade, who were randomized to a control group or an active group. Patients in the active group received PTX (1200 mg/day) on top of RAAS blockers. After 2 years of follow-up, the rate of progression of renal disease was reduced in the PTX group, which was accompanied by a decrease in proteinuria. This study was designed to evaluate renal disease progression as the primary outcome, with adequate power, sample size, and follow-up time, and the results provide new evidence on the bene cial effects of PTX on DKD progression.[24] This result similar to our study in terms of proteinuria reduction rather than duration.

There was a trend of reduction of serum creatinine and increase of eGFR during 6 month's treatment with pentoxyphyline from baseline but it did not reach statistical significance. In contrast in the control group there was statistically significant rise of serum creatinine and reduction of eGFR from baseline to 6 months after study. In a study observed that, after 2 years of follow-up, the rate of progression of renal disease was reduced in the PTX group, which was accompanied by a decrease in proteinuria. The smaller decrease of eGFR in the PTX group with respect to the control group showed a trend at 6 months and reached statistical signi cance after 1 year, suggesting that a longer duration of treatment with PTX is necessary to observe a therapeutic bene t on renal function.[24] Our study was limited by short follow-up period, which prevented it from making any inference regarding the ultimate effect of PTX on serum creatinine and eGFR.

In our study, urinary TNF-α decreased by 2.87ng/g after PTX administration, which was directly correlated with the change in uACR. In control group there was statistically insignificant rise of urinary TNF-α after 6 months from baseline. Previous studies with PTX have found similar results regarding urinary TNF-α.[25.26] But, it was not possible to draw conclusion from the present study whether urinary TNF-α decrease was part of the reduction in proteinuria or was a special effect of PTX. However, a previous study found that UAE was directly and independently associated with urinary TNF-α excretion, with no correlation between serum and urinary TNF-α, suggesting an intrarenal production of this cytokine.[8] Moreover, preceding studies found a signi cant reduction in urinary TNF-α levels in patients with DKD who received PTX, with a positive and signi cant correlation between the change in albuminuria and the change in urinary TNF-α.[15,24,26]

Adverse events were consistent with the known safety pro le of PTX obtained from a wide clinical experience for more than 30 years in patients with vascular disease, with and without diabetes and renal function impairment.[15,26,27] The most common adverse effects of PTX are gastrointestinal symptoms and dizziness.[28] Presumably, these effects of PTX may occur more in patients whose dosages are not tailored by degrees of renal dysfunction. A study observed a relatively high incidence of adverse effects, i.e., nausea, dyspepsia and diarrhea in 5 patients (23%) during the study period. They considered this could be ascribed to no reduction of PTX doses in patients with moderate renal dysfunction, which resulted in accumulation of PTX metabolites and gastrointestinal intolerance.[29] In the PREDIAN trial, the incidence of abdominal discomfort, flatus, dyspepsia, nausea and vomiting in patients treated with PTX was significantly higher than in the control group (21.9% versus 10.3%). these digestive symptoms were self-limited and disappeared when used continuously with proper dose adjustment beyond the first month.[24] During multidose pharmacokinetic studies, accumulation of active metabolites IV and V has been documented in patients with renal impairment. For that reason, dose reduction to 400 mg twice daily and 200–400 mg daily is advised for patients with

creatinine clearances between 30 and 80 and <30 mL/min, respectively.[30] In our study, PTX was initiated according to the eGFR. The most common secondary effects were transient, self-limited digestive symptoms that disappeared during the first month. The schedule of PTX administration based on an initial eGFR, the use of an extended-release formulation, and the administration with food are potential factors that could positively in uence on tolerability.

Limitations

We conducted this study in a single center with small sample size with short duration follow up.

Conclusion

The outcome of this study among patients with DN, stages 3–4 CKD was significant reduction of uACR after 6 months treatment with Pentoxifylline and Losartan along with other standard treatment with no significant reduction of serum creatinine or improvement of GFR. The additive antiproteinuric effect of Pentoxiphyline was not related to the decrease of BP or an improvement of metabolic control and was associated with a reduction of urinary TNF α excretion. These results were supportive of the renoprotective effects of Pentoxifylline in diabetic patients with nephropathy who are on optimum medical therapy.

Recommendations

In our study, we found that, effect of Pentoxifylline over DN was beneficial in reducing proteinuria. This effect of Pentoxifylline over DN needs to be evaluated further by large-scale, adequately powered, multicenter, prospective, placebo-controlled studies, with de nitive endpoints on ef cacy and safety.

Acknowledgements

The authors gratefully acknowledge the contribution of all doctors and staffs working in the Department of Nephrology, Chittagong Medical College Hospital.

Contribution of authors

MSA-Conception, acquisition data, interpretation of data, drafting & final approval.
SMI-Data analysis, critical revision & final approval.
SA-Interpretation of data, drafting & final approval.
MNM-Conception, design, interpretation of data, critical revision & final approval.
MNH-Design, critical revision & final approval.
PKD-Conception, data analysis, drafting & final approval.

Disclosure

All authors declared no conflict of interest.

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