Research Article (Araştırma makalesi)

The Effect of Pentoxifylline Treatment on Diabetic Nephropathy Progression

Pentoksifilin Tedavisinin Diyabetik Nefropati Progresyonuna Etkisi

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Özet

Amaç: Diabetik nefropati (DN) son dönem böbrek yetersizliğinin önemli bir nedenidir. Vasküler hastalıklarda kullanılan ve anti-inflamatuar özellikleri olan pentoksifilinin diyabetik nefropatide olumlu etkileri olabileceği öne sürülmüştür. Bu çalışmada DN nedeni ile takipte olan ve pentoksifilin kullanan hastaların tedavi öncesi ve sonrası dönemdeki böbrek fonksiyonları ve proteinürileri değerlendirilmiştir.

Gereç ve Yöntemler: Kliniğimizde takipte olup pentoksifilin (1200 mg/gün) tedavisi alan 36 diabetik nefropati hastası retrospektif olarak tarandı. Tedavi başlanmadan önceki 3. ve 6. ay; pentoksifilin tedavisinin 3., 6., 9. ve 12. aylardaki günlük proteinüri miktarı ve eGFR (estimated glomerular filtration rate, tahmini glomerüler filtrasyon hızı) değerleri kayıt edildi.

Bulgular: Çalışmaya alınan 36 hastanın ortalama yaşı 51.9±12.3 yıl, 12'si erkek ve 16'sı Anjiotensin dönüştürücü enzim (Angiotensin converting enzyme inhibitor, ACEİ) ya da Anjiotensin reseptör blokeri (Angiotensin receptor blocker, ARB) kullanıyordu. Pentoksifilini 23 hasta ≤6 ay (A grubu) 13 hasta >6 ay (B grubu) süre kullanmıştı. Proteinüri miktarı ve eGFR kaybı yönünden her iki grupta anlamlı farklılık saptanmadı.

Sonuç: Çalışmamızda diabetik nefropatili hastalarda 1 yıllık takip sırasında pentoksifilin tedavisinin proteinüri miktarı ve eGFR kaybına etkisi saptanamamıştır.

Anahtar kelimeler: Diabetik nefropati, Pentoksifilin, Proteinüri

Abstract

Objective: Diabetic nephropathy (DN) is an important cause of end stage renal disease. It has been suggested that pentoxifylline, which is used for the treatment of vascular diseases, has anti-inflammatory properties and may have positive effects on diabetic nephropathy. In this study, we aimed to investigate the effect of pentoxifylline treatment on renal functions and proteinuria levels in patients with DN.

Material and Methods: Thirty-six DN patients treated with 1200 mg/day pentoxifylline were screened retrospectively. Twenty-four-hour proteinuria and estimated glomerular filtration rate (eGFR) values were recorded at 3rd and 6th months before starting treatment and at 3rd, 6th and 12th months of pentoxifylline treatment.

Results: The average age was 51.9±12.3 years. In this patient cohort, 12 were male and 16 were using angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blockers (ARB). Twenty-three patients used pentoxifylline for less than 6 months (group A) and 13 patients used it for more than 6 months (group B). There was no difference between groups A and B regarding the amount of 24-hour proteinuria (Group A: 3.76±2.49 g/day, Group B: 4.72±3.20 g/day, p=0.423) and loss of eGFR (Group A: 37.98±31.2 ml/min, Group B: 34.00±29.99 ml/min, p=0.846).

Conclusion: In this study, the effect of pentoxifylline on proteinuria and eGFR loss was not observed in patients with diabetic nephropathy during 1-year follow-up.

Keywords: Diabetic nephropathy, Pentoxifylline, Proteinuria

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INTRODUCTION

Pentoxifylline is a nonspecific phosphodiesterase inhibitor and a methylxanthine derivative which is often used in the treatment of peripheral and cerebral vascular microcirculation disorders. In addition to its hemorheological effects, pentoxifylline also has antiproliferative and anti-inflammatory effects (1). Pentoxifylline competitively inhibits phosphodiesterase which in turn increases intracellular cAMP (cyclic adenosine monophosphate), activates protein kinase A, inhibits interleukin and tumor necrosis alpha synthesis and decreases inflammation (2). It also inhibits the increase of intercellular adhesion molecule-1 (ICAM-1), monocyte chemoattractant protein-1 (MCP-1) and osteopontin expression. In addition to antiproliferative effect, anti-inflammatory effects of pentoxifylline have been associated with a decrease in proteinuria and development of glomerular crescent, sclerosis and interstitial fibrosis (3). Moreover, pentoxifylline has been reported to be effective in diabetic nephropathy (4). In this study, diabetic nephropathy patients under pentoxifylline treatment were evaluated retrospectively in order to evaluate their renal functions and proteinuria during the follow-up period.

MATERIALS AND METHODS

Thirty-six patients with DN under pentoxifylline treatment (1200 mg/day) for peripheral artery disease were included in the study who were being followed up in our outpatient clinic. Proteinuria and eGFR values were obtained from the hospital records at the 3rd and 6th months before initiation of treatment and at the 3rd, 6th, and 12th months after the initiation. Patients on ACEI/ARB, insulin and other medications were recorded. Ethics committee approval is obtained from Cukurova University Ethics Comitee (Date: 04.03.2016, Session No: 51 Decision No: 22). Statistical analysis was performed using SPSS software (Version 25.0, SPSS Inc., Chicago, IL, USA). Chi-square, Student's T-test and Mann Whitney U tests were used. Logistic regression analysis was performed to investigate the effect of ACEI/ARB use in addition to pentoxifylline on the amount of proteinuria and e-GFR level.

RESULTS

Demographic data of the patients are presented in **Table 1**. In this cohort, the mean age of patients was 51.9±12.3 years, and 24 of the patients (66.7%) were female. The patients suffered from diabetes mellitus with an average of 11.3±9.2 and from hypertension with an average of 7.6±8.9 years. The average cigarette smoking among patients was 26.5±15.2 packages/year. Twenty-three patients used pentoxifylline for less than 6 months (group A) and 13 patients used it for more than 6 months (group B). Sixteen patients were under ACEI/ARB treatment, whereas 20 patients were under insulin treatment. The distribution of patients under ACEI/ARB or insulin treatment per gender and pentoxifylline treatment is presented in **Table 2**.

No statistically significant difference was found in the amount of proteinuria and eGFR levels at 6 and 3 months before the initiation of treatment in the whole cohort (p=0.657 for proteinuria; p=0.61 for proteinuria). As presented in **Table 3**, there was no statistically significant difference between proteinuria and eGFR levels of patients of groups A and B at 3 and 6 months

Table 1. Demographic data of patients

Variables		Mean±SD/Median n(%)
Age		51.9±12.3/55
Female/Male		24(66.7)/12(33.3)
Diabetes Mellitus period (year)		11.3 ± 9.2/10
Hypertension period (year)		7.6 ±8.9/5
Cigarette smoking (packages/year)		26.5±15.2/29
Pentoxifylline treatment period	≤ 6 months (Group A)	23 (63.9)
	> 6 months (Group B)	13 (36.1)
ACEI/ARB treatment		16 (44.4)
Insulin treatment		

ACEI/ARB: Angiotensin converting enzyme inhibitor/ Angiotensin receptor blocker, SD: Standard deviation

Table 2. Relationship between ACEI/ARB, insulin usage and pentoxifylline treatment

		ACEI/ARB		Insulin	
		No	Yes	No	Yes
		n	n	n	n
Gender	Female	14	10	11	13
	Male	6	6	5	7
Pentoxifylline treatment	≤6 months	12	11	11	12
	>6 months	8	5	5	8

ACEI/ARB: Angiotensin converting enzyme inhibitor/Angiotensin receptor blocker

Table 3. eGFR and proteinuria levels of patients using pentoxifylline for less than 6 months (Group A) and over 6 months (Group B) before and after pentoxifylline treatment

Time		Group A Proteinuria (g/day)	Group B Proteinuria (g/day)	p	Group A e-GFR (ml/min)	Group B e-GFR (ml/min)	p
6 months before	Mean±SD	4.42±3.00	6.40±3.50	0.135	47.91±35.93	47.65±35.36	0.897
	Median	3.380	7.710		36.400	33.450	
	Min-max	1.0-11.0	1.3-12.0		13.0-122.0	13.0-114.6	
3 months before	Mean±SD	3.98±2.31	6.41±2.97	0.066	50.42±37.15	43.40±30.65	0.660
	Median	3.900	7.000		36.700	31.200	
	Min-max	0.9-7.2	1.7-10.3		12.3-122.3	12.1-96.6	
Treatment	Mean±SD	3.60±2.32	5.59±3.53	0.070	42.33±29.95	40.59±27.49	0.871
	Median	2.500	6.000		36.700	33.000	
	Min-max	1.0-8.0	0.7-14.3		9.9-118.0	10.0-99.4	
After 6 months	Mean±SD	3.45±2.32	4.33±3.10	0.572	40.17±31.66	34.84±23.88	0.869
	Median	3.040	3.720		35.700	27.600	
	Min-max	0.3-7.3	0.5-11.3		7.3-110.7	8.4-81.3	
After 1 year	Mean±SD	3.76±2.49	4.72±3.20	0.423	37.98±31.22	34.00±29.99	0.846
	Median	3.600	4.674		29.400	23.800	
	Min-max	0.5-8.3	1.0-11.0		6.4-96.0	7.6-109.0	

eGFR: Estimated glomerular filtration rate

before treatment which demonstrates the unbias in the evaluation of post-treatment measurements. After 6 and 12 months of pentoxifylline treatment, no statistically significant difference was observed in terms of proteinuria and eGFR loss between Groups A and B. The relationship between duration, proteinuria and e-GFR of diabetic nephropathy patients using pentoxifylline is schematized in **Figure 1**.

Regression analysis was performed to evaluate the effect of pentoxifylline treatment in addition to RAAS blockade (Renin angiotensin aldosterone system block, the common name of ACEI or ARB treatments) to reduce proteinuria and ESRD progression (**Table 4**). In our study, ACEI/ARB use was found to be an independent risk factor only for eGFR. Although the amount of proteinuria was low in ACEI/ARB users in univariate analyses, the result of regression analysis was not statistically significant. In other words, according to the regression analysis performed in our study, the use of ACEI/ARB was not effective for proteinuria alone, however, it was found to be an independent risk factor for high eGFR.

DISCUSSION

In several studies conducted in patients with type 2 diabetes who developed DN, pentoxifylline was shown to have a renoprotective effect (3,4). However, these findings have not been confirmed by larger multicenter long-term studies (5).

The first sign of diabetic nephropathy is usually proteinuria which is defined as a risk factor for progression

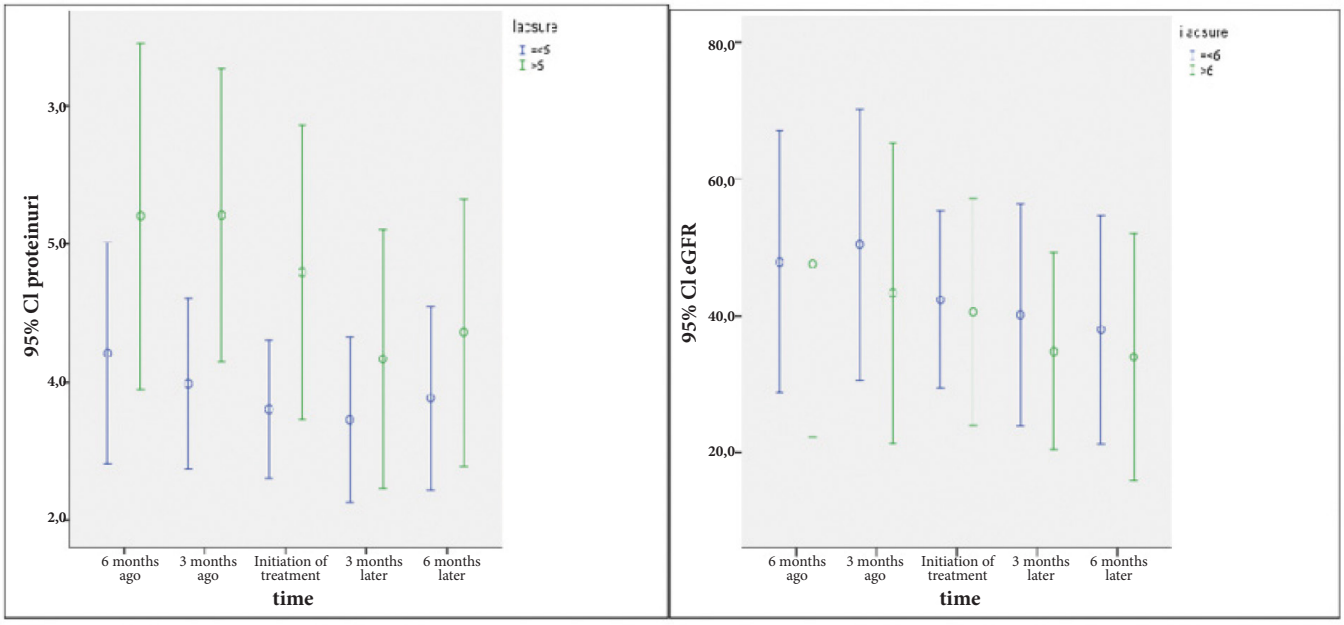

Figure 1. The relationship between duration, proteinuria and e-GFR in patients with diabetic nephropathy on pentoksfylline treatment

Table 4. Logistic regression analysis investigating the additional contribution of ACEI/ARB use in addition to pentoxifylline for eGFR and proteinuria 6 months and 1 year after treatment

Variables	B	S.E.	Wald	df	p	Odds Ratio	95% CI for EXP(B)	
							Lower	Upper
After 6 months Proteinuria (g/day)	-0.098	0.21	0.21	1	0.644	0.91	0.597	1.375
After 6 months eGFR (ml/min)	0.065	0.03	4.29	1	0.038	1.07	1.004	1.135
Constant	-1.91	1.37	1.96	1	0.161	0.147		
After 1 year Proteinuria (g/day)	-0.003	0.014	0.04	1	0.844	0.997	0.970	1.025
After 1 year e-GFR (ml/min)	0.083	0.063	1.76	1	0.185	1.087	0.961	1.229
Constant	-2.23	1.82	1.49	1	0.223	0.108		

eGFR: Estimated glomerular filtration rate, ACE. Angiotensin Converting Enzyme Inhibitor , ARB: Angiotensin Receptor Blocker

to chronic renal failure and reduction in proteinuria is associated with better renal survival. In the RENAAL study, in which losartan (angiotensin 2 antagonist) was administered to patients with DN, correlations between basal proteinuria or albuminuria level with renal survival have been shown (6).

In a Korean study evaluating the effect of pentoxifylline on the progression of diabetic nephropathy, it has been shown that proteinuria decreased significantly in the pentoxifylline group compared to the control group (3). Also, in the PREDIAN study, the renoprotective effects of pentoxifylline were investigated and it has been shown that pentoxifylline slowed down the progression with RAAS blockade in 24 months. A statistically significant difference for positive effect of pentoxifylline was shown after the first year of treatment (4). In our study, patients were observed for one year after pentoxifylline treatment, however, no positive effect on progression was observed when pentoxifylline was used alone or in combination with RAAS blockade. The fact that the study period is one year may have been the reason why the positive effect was not observed.

In a study conducted in Taiwan, the effect of pentoxifylline on the progression of end-stage renal disease has been studied, and it has been shown that the use of pentoxifylline reduced the progression to ESRD by 36% independent from RAAS blockade (7).

When compared to losartan 50 mg/day (29 DN patients), pentoxifylline 2x400 mg/day (30 DN patients) has been shown to decrease urinary albumin excretion and hsCRP more effectively at the end of 12 weeks, while blood pressure decreased more in the losartan group. Although the duration of the study is as short as 12 weeks, it may be important that pentoxifylline further reduced urinary albumin excretion without lowering blood pressure as much as losartan (8).

In a study, it has been reported that the anti-albuminuric and anti-inflammatory effect of pentoxifylline may be due to the decrease of TNF-α in serum and urine, the increase of Klotho level in serum and urine, and Klotho expression in renal tubular cells (9). In the present study, Klotho and TNF-α levels have not been measured.

In a meta-analysis in which 587 patients were included from eight studies, it has been shown that the combination of pentoxifylline and RAAS blocker had a positive effect on proteinuria and albuminuria, but had no effect on glycated hemoglobin (HgA1c), serum creatinine, creatinine clearance, systolic or diastolic blood pressure (10). In our study, no statistically significant difference was observed between groups of patients using pentoxifylline for longer or shorter than 6 months in terms of the annual loss in creatinine clearance. The effect of pentoxifylline on proteinuria and annual eGFR loss in non-diabetic patients with chronic kidney disease has not been demonstrated (11).

The limitations of our study are the small number of patients, the short follow-up period and the retrospective nature of the study, as well as the inability to standardize other individual factors that affect progression. In addition, in our study, it is known that 16 patients used ACEI/ARB agent 6 months before the initiation of pentoxifylline treatment. No dose change was made. The level of proteinuria before using ACEIs/ARBs is unknown.

CONCLUSION

In patients with diabetic nephropathy, no effect of pentoxifylline treatment for proteinuria and eGFR loss during 1-year follow-up was observed.

Conflict of Interest Statement: The authors of the article declare that there is no conflict of interest.

Contribution Rate Statement Summary: The authors declare that, they have contributed equally to the manuscript.

Ethical Approval: Ethics committee approval is obtained from Cukurova University Ethics Comitee (Date: 04.03.2016, Session No: 51 Decision No: 22). This study have been conducted in accordance with the Helsinki Declaration of Principles.

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