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# Pentoxifylline: A Promising Solution For Reducing Proteinuria In Type 2 Diabetes Patients

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## Abstract

**Objective:** To determine the effects of pentoxifylline on reducing proteinuria in diabetic patients.

**Methods:** A randomized placebo-controlled trial was conducted at the Nephrology department of Akbar Niazi Teaching Hospital, Islamabad and the Medicine department of Pakistan Ordnance Factory (POF) Hospital, Wah Cantt, Pakistan from January to June 2024. A total of 170 patients with type 2 diabetes on ACE inhibitors and ARBs but still having proteinuria over 500 mg/24 hours were enrolled in the study. 85 patients and placebo-treated volunteers formed the control group. Patients received 400 milligrams of oral pentoxifylline thrice daily. Proteinuria was measured for 24 hours at the onset of the experiment and during the initial quarter and half a year after pentoxifylline administration. In the other group, 85 healthy participants received a placebo.

**Results:** The mean age of the patients was 59.2±10.2 years (ranging; from 18 to 70 years), with 56.5% (n=96) male and 43.5% (n=74) female. Patients who consumed oral pentoxifylline decreased proteinuria significantly ($p \leq 0.05$). Proteinuria decreased over the initial three months were significant ($p \leq 0.05$).

**Conclusion:** According to trial data, pentoxifylline three times a day reduces proteinuria and prevents renal failure. The dosage does not affect the kidneys.

**Keywords:** Diabetes mellitus; Diabetic nephropathies; Hypertension; Kidney failure, Chronic; Pentoxifylline; Proteinuria.

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## Introduction

Increased blood glucose levels are a common metabolic condition collectively known as diabetes mellitus. Diabetes continues to be one of the leading causes of mortality and morbidity worldwide. Retinopathy, neuropathy, and nephropathy are late (secondary) problems associated with diabetes. Kidney failure (ESRD) is thought to be most frequently caused by diabetic nephropathy.[1] More therapy options are now available to slow the progression of the disease and improve renal function.

About 30% to 50% of all end-stage renal disease (ESRD), dependent kidney disorders require active therapy, which involves replacing kidney function. Consequences associated with type 2 diabetic nephropathy include hemodialysis, peritoneal dialysis, and renal transplantation. The most sensible approach to lessen patient expenses and suffering while delaying dialysis or kidney transplantation is to prevent ESRD.[2]

The worst risk factor for progression to the final stage of renal impairment in large-scale investigations including numerous diabetic patients is proteinuria.[3] Proteinuria in these patients needs to be reduced because of the increased risk of renal injury.[4] At the moment, proteinuria is treated with ACEs and ARBs.[5] As a result, reducing proteinuria can result in the greatest level of renal protection.[6] To accomplish this, multiple treatments are required almost always.[7]

According to recent studies, people with diabetes who still have normal renal function can experience less proteinuria when using pentoxifylline (PTX).[8] It is involved in the development of diabetic nephropathy and interstitial renal fibrosis.[9-11] Pentoxifylline's usage as an antiproteinuric medication has a solid scientific foundation, as evidenced by existing experimental data on humans and animals.[12-13]

Pentoxifylline appears to be able to preserve kidney function by further reducing proteinuria, which in turn minimizes cardiovascular problems.[14] The individuals have a cardiovascular death rate that is ten to twenty times greater than the general population.[15] Before hemodialysis, 60% to 90% of individuals with renal insufficiency had arterial hypertension.[16] In about 20% to 30% of these patients, congestive cardiac failure is the reason for death.

The study objective was to determine whether pentoxifylline, in addition to ACE and ARB therapy, was effective in lowering proteinuria among individuals having type 2 diabetes mellitus.

## Materials And Methods

This randomized placebo-controlled trial was conducted at the Nephrology department of Akbar Niazi Teaching Hospital, Islamabad and the Medicine department of Pakistan Ordnance Factory (POF) Hospital, Wah Cantt, Pakistan from January to June 2024. After getting approval from the institutional review board vide letter No. 49/IMDC/IRB-2023, Dated: 12 December 2023 and voluntary participation of the study participant, a total of 170 individuals suffering from type 2 diabetes who were receiving ACE inhibitors plus ARB treatment but still had proteinuria greater than 500 mg/24 hours were included in this trial. The sample size was determined by a 25% relative change with type I error of 5% and coefficient variation of 5.5%, and the minimum required sample for 80% power was 85 in each group.[6] Patients were excluded from the study if they had creatinine level > 2.0 mg/dL, systemic inflammatory history, immunological, or malignant diseases, or cardiovascular disease within the past 6 months. Additionally, treatment with immunosuppressive medications, use of pentoxifylline, or sildenafil citrate within the previous 3 months, pregnancy, breastfeeding, or aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels exceeding three times the upper normal limit.

A non-probability consecutive sampling method was used to enrol the patients in this trial. Patients were randomly divided into two groups i.e., pentoxifylline group (n=85; or experimental group) and placebo-controlled group (n=85) by computerized method. Allocation was concealed by placing assignments in sequentially numbered, sealed opaque envelopes, which were opened only after the enrolled patients required treatment allocation.

Three times a day, 400 mg of pentoxifylline was administered to the experimental group. The trial started with a 24-hour proteinuria assessment, and it was repeated after its first three months and six months. In the other group, 85 healthy participants received a placebo treatment which was identical starch tablets on the same schedule. An amnesia test, an objective examination, laboratory testing for metabolic parameters, and blood tests for proteinuria were administered to all patients and individuals in the control group over 24 hours. Patients were instructed not to modify their medications, diet, or physical activity throughout the study. Patients were monitored at 3 and 6 months during the treatment period to assess the outcome measurements. The primary endpoint was the change in proteinuria from baseline to the end of treatment, comparing the pentoxifylline group with the placebo group.

All efficacy and safety analyses were performed based on the intention-to-treat principle. Continuous variables are presented as mean ± standard deviation (SD), while categorical variables are reported as frequencies (percentages). The independent t-test was employed to compare continuous variables between groups, based on the assumption of normality, while the $\chi^2$ test was used for categorical data where applicable. The statistical test was two-tailed, with p-value < 0.05 considered significant. All analyses were conducted using SPSS v 23.

## Results

A total of 170 patients suffer from type 2 diabetes. Protein in urine was observed in these patients, but there was a reduction in the amount of protein in urine at the initial three months of the trial. The mean age of the patients was 59.2±10.2 years (ranging; from 18 to 70 years). There were 96 (56.5%) males and 74 (43.5%) females among the patients. The pentoxifylline was at an upper initial point of 5.6 g/24 hours, which decreased to 1.45 g/24 hours after three months of therapy (Fig. 1). Following a 6-month course of pentoxifylline treatment, the mean proteinuria level seen was 1.14 g/l; the highest was 2.1 g/l, with the lowest at 0.20 g/l (Fig. 2). Proteinuria was 124 mg at first, 143 mg in the second quarter, and 123 mg at the half-year mark, all of which are within the normal range. The comparison of protein in urine and leukocytes between the groups is shown in Table 1-4. It is evident from this study's analyses that males predominate more. Proteinuria values have decreased since the start of treatment with pentoxifylline. The value of pentoxifylline at the highest starting point of 5.6 g/24 hrs, decreased to 1.45 g/24 hours after three months of therapy. Following a half-year course of treatment with pentoxifylline, the mean level of urine having protein was 1.14 g/l; the highest was 2.1 g/l, and the lowest was 0.20 g/l. Protein urination was 124 mg at first, 143 mg in the second quarter, and 123 mg at the half-year mark, all of which are within the normal range.[6]

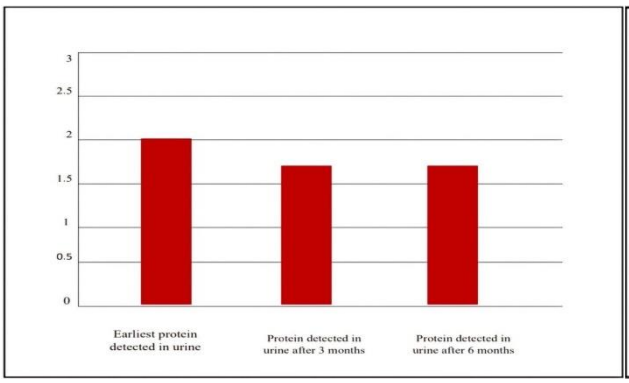


**Figure 1: Proteinuria after pentoxifylline treatment for diabetic nephropathy**

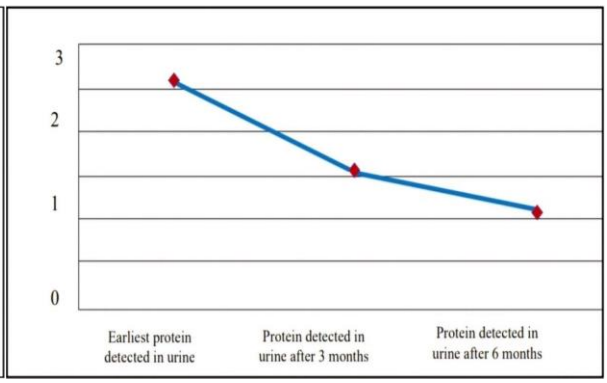


**Figure 2: Proteinuria after pentoxifylline treatment for diabetic nephropathy**

**Table 1: Initial protein in urine between the groups, n=170**

| Variables | N | Mean | SD | SE Mean | 95% confidence interval | | t-value | p-value |
|---|---|---|---|---|---|---|---|---|
| | | | | | Lower | Upper | | |
| **Earliest proteinuria in the pentoxifylline group** | 85 | 169.7 | 39.2 | 4.3 | 148.92 | 165.34 | 38.09 | .0001 |
| **Earliest proteinuria in the placebo group** | 85 | 2.70 | 1.2 | 0.14 | | | | |
| **Difference** | - | 157.13 | 36.90 | 4.13 | | | | |

*SE: Standard error, t: independent t-test*

**Table 2: Protein in urine after 3 months between the groups, n=170**

| Variables | N | Mean | SD | SE Mean | 95% confidence interval | | t-value | p-value |
|---|---|---|---|---|---|---|---|---|
| | | | | | Lower | Upper | | |
| **The earliest proteinuria in the pentoxifylline group** | 85 | 171.66 | 33.26 | 3.71 | 151.23 | 168.0 | 44.68 | .0001 |
| **Earliest proteinuria in the placebo group** | 85 | 1.57 | 0.63 | 0.07 | | | | |
| **Difference** | - | 170.08 | 32.63 | 3.64 | | | | |

*SE: Standard error, t: independent t-test*

**Result 3: Protein in urine in the initial period and at 3 and 6 months between groups, n=170**

| Variables | N | Mean | SD | SE Mean | 95% confidence interval | | t-value | p-value |
|---|---|---|---|---|---|---|---|---|
| | | | | | Lower | Upper | | |
| **Earliest proteinuria in the pentoxifylline group** | 85 | 172.18 | 32.76 | 3.68 | 152.78 | 166.70 | 45.47 | .0001 |
| **Earliest proteinuria in the placebo group** | 85 | 1.16 | 1.76 | 0.2 | | | | |
| **Difference** | - | 171.02 | 31.0 | 3.68 | | | | |

*SE: Standard error, t: independent t-test*

**Table 4: White blood cells between the groups, n=170**

| Variables | N | Mean | SD | SE Mean | 95% confidence interval | | t-value | p-value |
|---|---|---|---|---|---|---|---|---|
| | | | | | Lower | Upper | | |
| WBC in the pentoxifylline group | 85 | 7.94 | 1.49 | 0.17 | -1.99 | -0.42 | 3.02 | .002 |
| WBC in the placebo group | 85 | 9.24 | 1.48 | 0.40 | | | | |
| Difference | - | -1.30 | 0.01 | 0.24 | | | | |

## Discussion

Within the parameters of this investigation, contrasting the laboratory analysis values between the placebo-treated patients and the group of patients receiving pentoxifylline. Based on the analysis's findings, the proteinuria readings in patients receiving therapy were significantly lower than those in the patient group receiving no therapy. A significant difference is also evident when comparing the leukocyte values between the placebo group and the experimental group, as indicated by $p = 0.002$.

According to the findings, there is a significant difference between the erythrocyte counts of patients receiving therapy and the placebo group, with $p = 0.032$. Hemoglobin levels in patients receiving treatment with pentoxifylline do not significantly differ from those of placebo patients, in contrast to leukocyte and erythrocyte values.

Proteins ($p = 0.019$) and uric acid ($p = 0.0001$) are in 4 cases. Transaminase levels (Alanine transaminase; $p = 0.372$) and Aspartate transaminase levels were the laboratory analysis results that did not show a statistically significant difference among patients given pentoxifylline and placebo patients. Albumin level ($p = 0.601$), AST level ($p = 0.471$), cholesterol level ($p = 0.064$), and triglyceride level ($p = 0.060$). It may be observed that an insignificant difference was seen among these patients.

Leukocytes, red blood cells, hematocrit, creatinine levels, protein content in general, and uric acid were found insignificant. The laboratory findings, including ALT levels, remained stable. Additionally, AST, albumin, cholesterol, and triglyceride levels, were part of the analysis.

## Conclusions

Following therapy via pentoxifylline, individuals who had insulin resistance and renal insufficiency experienced a significant decrease in proteinuria or protein loss in the urine. Even though ACE or ARB was administered to all of these patients, it is possible that ACE or ARB was the primary cause of the protein reduction. The study draws the conclusion that pentoxifylline is effective in reducing proteinuria and averting renal failure based on the trial data. The dosage that was used has no harmful effects on the kidneys.

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**Contributions:**
J.K.K, S.A.A.S, - Conception of study
- Experimentation/Study Conduction
J.K.K, M.A, R.Y, W.S.B, M.F.U.H - Analysis/Interpretation/Discussion
M.A, S.A.A.S, W.S.B, M.F.U.H - Manuscript Writing
J.K.K, R.Y - Critical Review

All authors approved the final version to be published & agreed to be accountable for all aspects of the work.