# *The Potential Nephro-protective Effect of Folic Acid and/or Pentoxifylline on Patients with Chronic Kidney Disease*

NCT05284656

**10-6-2025**

## Introduction

Chronic kidney disease (CKD) is a worldwide public health problem, with adverse outcomes of kidney failure, cardiovascular disease (CVD), and premature death. ***(Andrew S.,et al,2005).***

Chronic kidney disease (CKD) affects between 8% and 16% of the population worldwide and is often under recognized by patients and clinicians. Defined by a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 $m^2$, albuminuria of at least 30 mg per 24 hours, or markers of kidney damage (eg, hematuria or structural abnormalities such as polycystic or dysplastic kidneys) persisting for more than 3 months.***( Teresa K. Chen ,et al,2019).***

Kidney damage refers to pathologic abnormalities either suggested by imaging studies or renal biopsy, abnormalities in urinary sediment, or increased urinary albumin excretion rates. ***.( Inker LA,et al,2019).***

To facilitate assessment of CKD severity, the National Kidney Foundation developed criteria as part of its Kidney Disease Outcomes Quality Initiative (NKF K/DOQI) to stratify CKD patients :

Stage 1: normal eGFR R 90 mL/min per 1.73 m2 and persistent albuminuria

Stage 2: eGFR between 60 to 89 mL/min per 1.73 m2

Stage 3: eGFR between 30 to 59 mL/min per 1.73 m2

Stage 4: eGFR between 15 to 29 mL/min per 1.73 m2

Stage 5: eGFR less than 15 mL/min per 1.73 m2 or end-stage renal disease ***.( Thomas, et al,2008)***

The best available method to estimate GFR is the equation from the Modification of Diet in Renal Disease (MDRD) study. The MDRD equation adjusts for 4 variables: body-surface area, race, gender, and age. GFR is expressed as mL/min/1.73m2; race is categorized as either black or not black.

Original MDRD study equation

$GFR = 186 \times (scr)^{-1.154} \times (age)^{-0.203} \times 0.742$ (if the patient is female) or x 1.212 (if the subject is black)

2005 re-expression*

GFR = 175 x (standardized scr) $^{-1.154}$ x(age) $^{-0.203}$ x 0.742 (if the patient is female) or 1.212 (if black)

Age in years,Weight in kilograms, and serum creatinine (Scr) in milligrams per deciliter.***( laurence E., 2006).***

That nutrient loss because of diet restriction and chronic inflammation contributed by CKD itself may stimulate progression in advanced chronic kidney disease. Folic acid was then selected as a nutrient intervention. In the mean time, pentoxifylline was well studied in this field for its anti-inflammatory effects***( Hsun Yang, et al,2019).***

Pentoxifylline (PTF) is a methylxanthine derivative that functions in vivo as a phosphodiesterase inhibitor. It was primarily used to treat patients with peripheral arterial disease. PTF appears to improve circulation through its ability to alter erythrocyte deformability and enhances capillary microcirculation. This hemorheological property and the potential capacity in decreasing intraglomerular pressure has led to recent interest in PTF as a therapeutic agent in patients with kidney disease. In addition to these properties, PTF has an effect on inflammation, oxidative stress and endothelial function***( Marian G, et al,2012).***

Pentoxifylline is known to inhibit the production of TNF-α , which is an important inflamatory mediator with a wide spectrum of activity, predominantly produced by mononuclear cells. Pentoxifylline is also an active inhibitor of already formed TNF. There is also evidence that pentoxifylline may influence other inflammatory cytokines, such as inhibition of IL-1 and IL- 6***( Hassan, et al,2014)***

**AIM OF THE WORK**

The aim of this study is to evaluate the effect of administration of folic acid and /or pentoxifylline on patients with chronic kidney disease (CKD).

**PATIENTS AND METHODS:**

**Study design:** Open labeled, Paralled, Randomized, Prospective, Controlled study.

**Setting:** Nephrology Clinics, Ain Shams University Hospitals, Ain Shams University, Cairo, Egypt.

**Timing:** For 6 months from the start of the study.

**Ethical Approval:** The study design will be approved by the Ethics Medical Committee of Ain Shams University Hospital or Ethical Committee in Faculty of Pharmacy (Girls), Al-Azhar University.

**Sample size:**

According to sample size calculation by Community ,Environmental and Occupational Medicine Department at Faculty of Medicine Ain Shams University, Eighty patients with chronic kidney disease (CKD) stages 3-5 will be enrolled in the study

Patients will be randomized into four groups each group includes 20 patients:

***Control Group***: 20 patients will receive their standard therapy only.

***Tested Group I***: 20 patients will receive folic acid 5 mg per day with their standard therapy for 6 months.

***Tested Group II***: 20 patients will receive Pentoxifylline ( TRENTAL® Tablets, 400 mg) twice daily with their standard therapy for 6 months.

***Tested Group III***: 20 patients will receive combination therapy of folic acid5 mg per day and pentoxifylline ( TRENTAL® Tablets, 400 mg) twice daily with their standard therapy for 6 months

**Patients eligible for the study fulfilled the following inclusion criteria and free from exclusion criteria:**

**Inclusion criteria:**

1. Patients who have chronic kidney disease(CKD) stages 3-5
2. Aged between18 - 60 years old.
3. Both sexes.
4. Stable clinical condition defined as no hospitalizations or cardiovascular events within the 3 months before screening
5. Stable renal function (baseline serum creatinine had to have not increased by 50% in the 3 months before screening)
6. No changes in concomitant medication during the study.
7. Patients who accept to participate in the study.

**Exclusion criteria:**

1. Pregnant women
2. Current use of PTF
3. Contraindication to use of PTF drug: history of PTF or theophylline allergy, history of severe retinal hemorrhage or recent cerebral hemorrhage
4. Those with active infections or inflammatory diseases or HIV infection

5. Those with chronic liver disease .
6. Patients who had received immunosuppressive therapy
7. Non-compliant patients

**Methods:**

**All Patients will be subjected to the following:**

1. Informed consent
2. History taking and Clinical examination
3. Laboratory evaluation including:

A- Serum creatinine

B- Urine analysis

C- Complete blood picture

D- Serum ferritin

E- Calcium, Phosphorous.

F-Abdominal Ultrasonography

g-Protein /creatinine ratio

All markers will be measured at baseline , after 3 months and after 6 months

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