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Serum α-Klotho as a Predictive Biomarker of Oxidative Stress and Declining Glomerular Function in Chronic Kidney Disease Patients: A Case-Control Study

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ABSTRACT

Background: Chronic kidney disease (CKD) is a progressive disorder characterized by declining renal function, increased oxidative stress, and metabolic disturbances. α-Klotho, an anti-aging protein predominantly expressed in the kidney, has emerged as a potential biomarker of renal dysfunction and oxidative stress. This study evaluated serum α-Klotho levels and their association with oxidative stress markers and renal function in patients with CKD.

Methods: A hospital-based observational case-control study included 90 participants (50 CKD patients and 40 healthy controls). Clinical assessment and biochemical investigations, including fasting blood sugar, serum urea, creatinine, electrolytes, total protein, and eGFR, were performed. Serum α-Klotho was estimated by ELISA, while TOL and TAC were measured using standard methods. Data were analyzed using SPSS version 20.0.

Results: CKD patients had significantly higher serum α-Klotho (2.59 ± 0.98 vs. 0.24 ± 0.09 ng/mL) and TOL (1.96 ± 1.01 vs. 0.05 ± 0.02 ng/mL), whereas TAC was significantly lower (281.80 ± 78.0 vs. 862.82 ± 51.86 µM) compared with controls (all $p<0.01$). Serum α-Klotho showed a significant positive correlation with fasting blood sugar ($r=0.352$, $p=0.012$), while no significant correlation was observed with eGFR ($r=-0.065$, $p=0.648$). Linear regression analysis revealed no significant independent predictors of serum α-Klotho.

Conclusion: CKD is associated with increased oxidative stress, reduced antioxidant capacity, and altered serum α-Klotho levels. Although α-Klotho was not significantly associated with eGFR, its relationship with oxidative stress suggests its potential role as a complementary biomarker in CKD.

Key-words: Chronic kidney disease; α-Klotho; Oxidative stress; Total oxidant load; Estimated glomerular filtration rate (eGFR)

INTRODUCTION

Chronic kidney disease (CKD) is a major global public health challenge. It is characterized by kidney damage or a sustained reduction in glomerular filtration rate (GFR) to <60 mL/min/1.73 m² for at least three months, irrespective of the underlying cause [1,2].

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This condition is characterized by structural and/or functional abnormalities in the kidneys, often accompanied by clinical markers such as persistent albuminuria, abnormal imaging findings, or histopathological changes. CKD encompasses a wide spectrum of etiologies including diabetic nephropathy, hypertensive nephrosclerosis, glomerulonephritis, and polycystic kidney disease, among others.

Globally, CKD has emerged as a leading cause of morbidity and mortality, with an estimated prevalence of 13.4% (ranging from 11.7% to 15.1%), affecting approximately 700 million individuals worldwide [3]. Its increasing incidence is driven largely by aging populations and the rising burden of non-communicable

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diseases such as diabetes mellitus and hypertension. In developing countries, including India, the prevalence of CKD is particularly concerning due to limited access to early detection and renal replacement therapies. In India, the estimated prevalence is about 800 cases per million population, and annually, around 150–200 individuals per million progress to end-stage renal disease (ESRD), necessitating dialysis or kidney transplantation [4,5]. This not only imposes a substantial clinical burden but also strains healthcare infrastructure and economic resources, highlighting the urgent need for early diagnostic markers and preventive strategies.

Beyond progressive loss of renal function, CKD is associated with systemic complications including cardiovascular disease, anemia, mineral and bone disorders, electrolyte imbalance, and metabolic abnormalities, all of which contribute to increased morbidity and mortality [6].

The pathogenesis of CKD involves hemodynamic alterations, chronic inflammation, oxidative stress, endothelial dysfunction, activation of the renin-angiotensin-aldosterone system, and accumulation of uremic toxins, resulting in progressive nephron loss and renal fibrosis [7].

Among the many pathophysiological mechanisms implicated in CKD, oxidative stress (OS) has gained recognition as a pivotal factor contributing to both disease initiation and progression, as well as its associated systemic complications [6,8]. Oxidative stress is defined as a state of physiological imbalance resulting from the overproduction of reactive oxygen species (ROS) that overwhelms the endogenous antioxidant defense mechanisms. These ROS, including superoxide anions, hydrogen peroxide, and hydroxyl radicals, are highly reactive molecules capable of inflicting damage on cellular lipids, proteins, and nucleic acids.

Oxidative stress contributes to endothelial dysfunction, tubular injury, glomerular damage, and progressive renal fibrosis, thereby accelerating CKD progression. These findings highlight the need for reliable biomarkers that reflect oxidative stress and disease severity [9].

A novel focus in recent nephrology research has been the anti-aging protein α-Klotho, a transmembrane protein predominantly expressed in the distal convoluted tubules of the kidneys [10,11]. The Klotho gene, first identified by Kuro-o *et al.* in 1997, encodes this protein, which exists in membrane-bound and soluble forms. Soluble α-Klotho, generated by proteolytic cleavage or alternative splicing, exerts hormone-like effects and is measurable in serum and urine [12,13].

Physiologically, α-Klotho functions as a co-receptor for fibroblast growth factor 23 (FGF23), regulating phosphate excretion and vitamin D metabolism [14,15]. It also modulates calcium and sodium reabsorption via TRPV5 and ROMK1 channels and exhibits antioxidant, anti-inflammatory, and anti-apoptotic effects [16-18]. Notably, α-Klotho expression is reduced early in CKD progression, and its deficiency is associated with vascular calcification, accelerated aging, and cardiovascular morbidity [13,14,19].

In animal models and clinical studies, α-Klotho deficiency has been shown to promote renal fibrosis, inflammation, and oxidative stress [20,21]. Mechanistically, α-Klotho activates FOXO transcription factors, upregulates superoxide dismutase (SOD), and suppresses the insulin/IGF-1 signaling pathway, enhancing cellular resistance to oxidative injury [7,20]. Additionally, α-Klotho inhibits NF-κB signaling, reducing the expression of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-12 [22,23].

MATERIALS AND METHODS

Study Design and Setting- This was a hospital-based observational case-control study conducted over a period of six months in the Department of Biochemistry, in collaboration with the Department of Nephrology, SCB Medical College and Hospital, Cuttack, Odisha, India.

Study Population- The study included 90 participants divided into two groups: 50 patients diagnosed with CKD, representing the case group, and 40 age- and sex-matched healthy volunteers, forming the control group. CKD was diagnosed based on KDIGO guidelines, with a GFR < 60 mL/min/1.73 m² for ≥3 months or markers of kidney damage.

Inclusion Criteria

1. Adults aged 18 years and above.
2. Clinically diagnosed cases of CKD of any stage, irrespective of etiology (e.g., diabetic nephropathy, hypertensive nephrosclerosis).
3. Patients under conservative management or maintenance hemodialysis.

doi: 10.21276/SSR-IIJLS.2026.12.4.17

Exclusion Criteria

1. Patients diagnosed with endocrine disorders (other than diabetes mellitus).
2. Individuals with systemic autoimmune diseases (e.g., lupus nephritis).
3. Chronic smokers and individuals with a history of alcohol abuse.
4. Participants currently taking antioxidant supplements, steroids, or immunosuppressive therapy.

Data Collection and Clinical Parameters- Demographic details and clinical history were documented using a structured proforma. Anthropometric measurements such as height, weight, and body mass index (BMI) were recorded using calibrated instruments. Blood pressure and pulse rate were measured using standard procedures. All measurements were taken in a standardized setting to reduce inter-observer variability.
Venous blood (5 mL) was collected from each participant after overnight fasting (8–10 hours) under aseptic precautions. Samples were processed within 1 hour of collection. Serum was separated by centrifugation at 3000 rpm for 10 minutes and stored at −20°C until further analysis.

Biochemical Investigations- Routine biochemical tests were performed using an automated biochemistry analyzer and commercially available kits:

- **Fasting blood sugar (FBS)**– Glucose oxidase-peroxidase method
- **Serum urea**– Urease-GLDH method
- **Serum creatinine**– Modified Jaffe's kinetic method
- **Serum electrolytes**– Ion-selective electrode method
- **Serum total protein**– Biuret method

Estimated glomerular filtration rate (eGFR) was computed using the Cockcroft-Gault equation:

CCr (mL/min) = × 0.85 (if female)

Measurement of Special Parameters

- **Serum α-Klotho levels (ng/mL)** were determined using a high-sensitivity sandwich ELISA kit (Evolis Twin Plus, Bio-Rad Laboratories). The assay had an intra-assay and inter-assay coefficient of variation <10%.
- **Total oxidant load (ng/mL)** was estimated by the Ferrous Oxidation-Xylenol Orange Version 2 (FOX_2) method, which detects hydroperoxides via ferrous ion oxidation in an acidic medium.
- **Total antioxidant capacity (µM)** was assessed using the Ferric Reducing Ability of Plasma (FRAP) assay, which measures the reduction of ferric-tripyridyltriazine to ferrous form at low pH.

Statistical Analysis- Data were analyzed using IBM SPSS Statistics version 20.0. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as frequencies and percentages. Comparisons between groups were performed using the unpaired Student's t-test. Pearson's correlation and linear regression analyses were used to evaluate the association between serum α-Klotho, oxidative stress markers, and eGFR. A *p*-value of <0.05 was considered statistically significant.

Ethical Considerations- Ethical clearance was obtained from the Institutional Ethics Committee (IEC/IRB No. 805/11.3.2019) prior to study initiation. Written informed consent was obtained from all participants before enrollment. The study was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

Table 1 presents the demographic, clinical, and biochemical characteristics of the study participants. Compared with healthy controls, patients with CKD had significantly higher age, male predominance, body weight, BMI, systolic blood pressure, fasting blood sugar, serum urea, and serum creatinine, while eGFR was significantly lower ($p < 0.05$ for all comparisons).
Table 2 compares the electrolyte, protein, serum α-Klotho, and oxidative stress profiles between CKD patients and healthy controls. CKD patients exhibited significantly lower serum sodium, potassium, calcium, total protein, and total antioxidant capacity, while serum α-Klotho and total oxidant load were significantly higher than those of the control group ($p< 0.01$ for all variables). These findings indicate marked electrolyte imbalance, impaired nutritional status, and increased oxidative stress in CKD patients.

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Table 1: Demographic, Clinical and Biochemical Characteristics of the Study Participants (N = 90)

Variable	CKD Group (n = 50)	Control Group (n = 40)	p-value
Age (years)	48.72 ± 10.98	42.60 ± 11.08	0.011
Male, n (%)	38 (76%)	15 (37.5%)	<0.01
Body weight (kg)	65.98 ± 10.07	60.22 ± 7.20	<0.01
BMI (kg/m²)	27.23 ± 4.19	25.11 ± 1.95	<0.01
SBP (mmHg)	120.00 ± 6.96	116.45 ± 5.62	0.002
Fasting blood sugar (mg/dL)	121.10 ± 30.22	92.45 ± 16.80	<0.01
Serum urea (mg/dL)	98.48 ± 23.84	25.28 ± 6.67	<0.01
Serum creatinine (mg/dL)	7.44 ± 2.88	0.94 ± 0.26	<0.01
eGFR (mL/min/1.73 m²)	9.58 ± 6.01	95.37 ± 30.37	<0.01

Table 2: Electrolyte, Protein, Serum α-Klotho and Oxidative Stress Profile of the Study Participants (N = 90)

Parameter	CKD Group (n = 50)	Control Group (n = 40)	p-value
Serum sodium (mmol/L)	121.26 ± 9.21	138.44 ± 2.92	<0.01
Serum potassium (mmol/L)	1.95 ± 0.54	4.23 ± 0.55	<0.01
Serum calcium (mmol/L)	0.65 ± 0.26	1.12 ± 0.12	<0.01
Total protein (g/dL)	3.48 ± 0.47	5.95 ± 0.81	<0.01
Serum α-Klotho (ng/mL)	2.59 ± 0.98	0.24 ± 0.09	<0.01
Total oxidant load (ng/mL)	1.96 ± 1.01	0.05 ± 0.02	<0.01
Total antioxidant capacity (µM)	281.80 ± 78.00	862.82 ± 51.86	<0.01

Table 3 presents the correlation of serum α-Klotho with selected clinical and biochemical parameters. In CKD patients, α-Klotho showed a non-significant negative correlation with eGFR and a significant positive correlation with fasting blood sugar. In healthy controls, α-Klotho was positively correlated with total protein and negatively correlated with serum sodium.

Table 3: Correlation of Serum α-Klotho with Clinical and Biochemical Parameters

Study Group	Variable	Correlation Coefficient (r)	p-value
CKD (n = 50)	eGFR	-0.065	0.648
	Fasting blood sugar	+0.352	0.012
Control (n = 40)	Serum total protein	+0.380	0.016
	Serum sodium	-0.234	0.033

Table 4 presents the linear regression analysis of eGFR, TOL, and TAC with serum α-Klotho in CKD patients. Although TOL showed a positive association and eGFR and TAC showed negative associations, none were statistically significant ($p > 0.05$).

Fig. 1 presents a bar chart comparing serum α-Klotho, TOL, and TAC between CKD patients and controls (N = 90), revealing elevated α-Klotho and TOL levels but markedly reduced TAC in the CKD g roup, highlighting a pronounced oxidative imbalance.

Table 4: Linear Regression Summary – Predictors of α-Klotho in CKD Group (n = 50)

Predictor	Regression Coefficient (β)	p-value
eGFR	-0.070	0.577
Total Oxidant Load	+0.489	0.169
Total Antioxidant Capacity	-0.173	0.556

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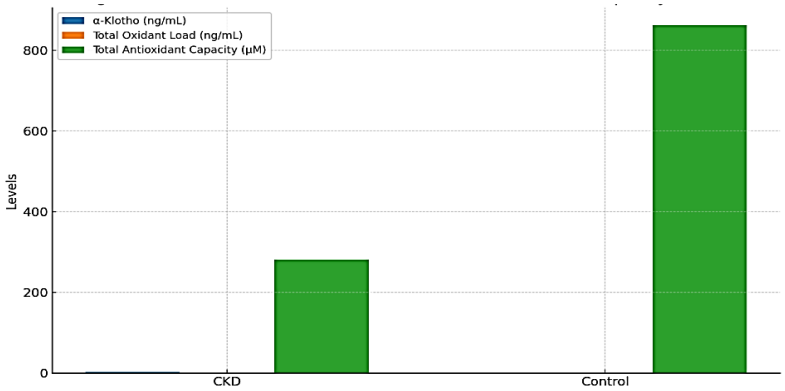

Fig. 1: Serum α-Klotho, Oxidant Load, and Antioxidant Capacity (N = 90)

Fig. 2 shows a scatter plot of α-Klotho versus eGFR in CKD patients (n = 50), where no evident linear correlation was observed, supporting the statistical finding of a weak and non-significant association between α-Klotho and glomerular function.

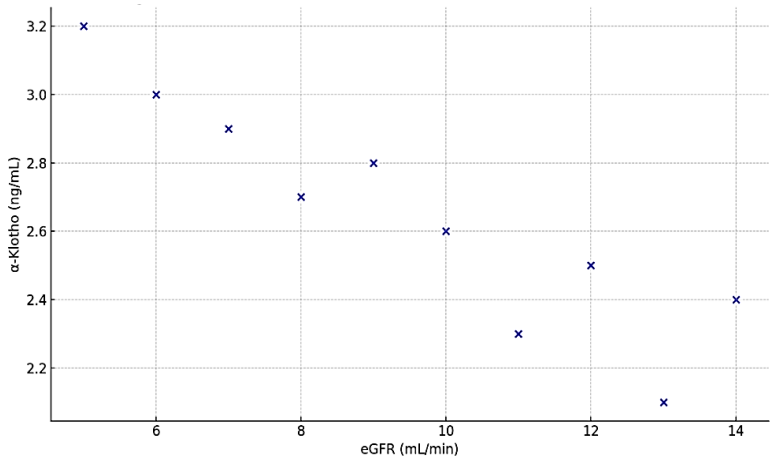

Fig. 2: Scatter Plot of α-Klotho vs eGFR in CKD Patients (n = 50)

Fig. 3 displays a correlation heatmap among key biomarkers (FBS, eGFR, α-Klotho, TOL, and TAC) in the CKD group (n = 50), demonstrating a significant positive correlation between fasting blood sugar and α-Klotho, weak or inverse relationships between eGFR and both Klotho and TOL, and a strong inverse correlation between TOL and TAC, collectively underscoring the multifactorial regulation of Klotho in CKD and its potential link to metabolic and oxidative stress.

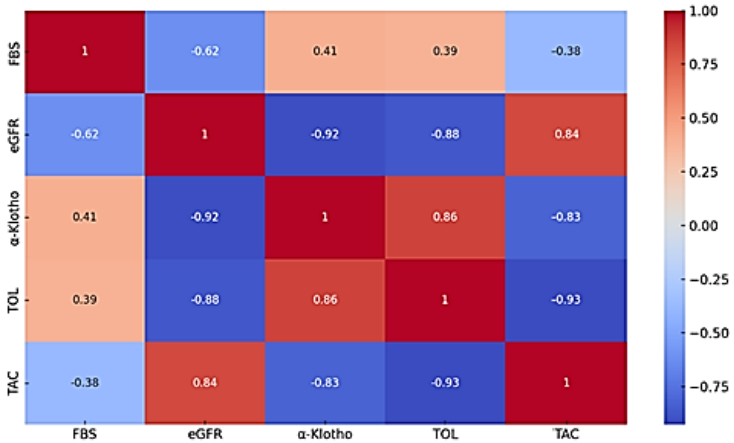

Fig. 3: Correlation Heatmap of Biomarkers in CKD Group (n = 50)

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DISCUSSION

The present study investigated serum α-Klotho levels in patients with CKD and evaluated their association with oxidative stress markers and renal function. The findings demonstrated significantly elevated serum α-Klotho levels in CKD patients compared with healthy controls, accompanied by increased total oxidant load (TOL) and markedly reduced total antioxidant capacity (TAC). Despite these biochemical alterations, serum α-Klotho showed only a weak and statistically non-significant correlation with estimated glomerular filtration rate (eGFR) [24-27].

Previous studies have consistently reported that α-Klotho is an important renoprotective protein involved in maintaining phosphate homeostasis, suppressing oxidative stress, and reducing inflammation. Shimamura *et al.* [5] demonstrated that soluble α-Klotho levels decline during the early stages of CKD and suggested its utility as an early biomarker of renal dysfunction. Similarly, Hu *et al.* [28] reported that Klotho deficiency is an early event in renal injury and contributes to CKD progression through enhanced oxidative stress, inflammation, and fibrosis. In contrast, the present study observed significantly elevated circulating α-Klotho levels in CKD patients. This paradoxical elevation may represent a compensatory response to persistent oxidative stress and renal injury through enhanced shedding of membrane-bound α-Klotho or impaired renal clearance.

The present study also demonstrated significantly increased TOL and markedly reduced TAC in CKD patients, confirming the presence of severe oxidative stress. Persistent oxidative stress is a well-recognized contributor to renal injury through endothelial dysfunction, tubular damage, inflammation, and progressive fibrosis. The observed increase in circulating α-Klotho may therefore represent an endogenous protective mechanism aimed at counteracting oxidative injury and limiting disease progression. Similar protective roles of α-Klotho against oxidative stress have been reported through suppression of reactive oxygen species generation and preservation of cellular antioxidant defenses [7,34,36].

A significant positive correlation between fasting blood sugar and serum α-Klotho was observed, suggesting that metabolic disturbances may influence Klotho regulation. Chronic hyperglycemia and oxidative stress have been shown to alter Klotho expression through inflammatory signaling pathways, indicating a close interaction between metabolic status and Klotho homeostasis [29–35].

Although serum α-Klotho levels were significantly elevated, their association with eGFR remained weak and statistically insignificant. This finding may be explained by the predominance of advanced CKD patients in the study population, where compensatory mechanisms, persistent inflammation, oxidative stress, and altered Klotho metabolism may obscure a direct relationship with renal function. Furthermore, circulating α-Klotho concentrations may not solely reflect renal production but may also be influenced by extra-renal expression and reduced clearance in advanced CKD.

The clinical significance of circulating α-Klotho in CKD therefore remains uncertain. While Shimamura *et al.* [5] and Akimoto *et al.* [26] reported reduced soluble α-Klotho levels with worsening renal function, Devaraj *et al.* [27] demonstrated elevated circulating α-Klotho concentrations in patients with CKD, supporting the possibility of compensatory upregulation or impaired renal elimination. In addition, chronic inflammation and oxidative stress may stimulate α-Klotho expression in extra-renal tissues, including vascular endothelium and parathyroid glands, thereby contributing to altered circulating concentrations [29–35].

Overall, the findings of the present study suggest that serum α-Klotho reflects not only renal dysfunction but also oxidative stress and metabolic imbalance. Therefore, α-Klotho may be better regarded as a complementary biomarker of systemic oxidative stress rather than a direct surrogate marker of glomerular filtration alone. Further multicentric prospective studies with larger sample sizes, stage-wise stratification, and longitudinal follow-up are required to establish the diagnostic and prognostic utility of serum α-Klotho in patients with chronic kidney disease.

LIMITATIONS

1. The study sample size was relatively small and derived from a single center, limiting generalizability.
2. Cross-sectional design prevents inference of causality or temporal trends in α-Klotho or oxidative stress markers.
3. The CKD group included patients across various stages without stratification, which may have diluted stage-specific trends.

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4. Potential confounding factors such as medication use, dietary intake, and dialysis status were not fully controlled.

STRENGTHS

1. Simultaneous assessment of α-Klotho, oxidative stress (TOL), and antioxidant capacity (FRAP) offers a comprehensive view of CKD-associated biochemical alterations.
2. Use of standardized and sensitive ELISA assays for biomarker quantification adds robustness to the findings.
3. Age- and sex-matched control group enhances internal validity.

CONCLUSIONS

This study provides compelling evidence that CKD patient's exhibit significantly elevated serum α-Klotho levels in parallel with marked oxidative stress and a pronounced reduction in antioxidant capacity. The paradoxical elevation of α-Klotho may signify a compensatory physiological adaptation to ongoing renal and systemic injury, particularly oxidative and inflammatory stressors that are hallmark features of CKD. Despite α-Klotho's renoprotective and anti-aging roles, its weak and statistically insignificant correlation with eGFR observed in this study suggests that it may not serve as a direct surrogate of glomerular function in advanced stages. Rather, its elevation could reflect systemic stress burden more than renal clearance impairment. Our findings, therefore, reinforce the emerging paradigm of α-Klotho not merely as a passive marker of renal decline, but as a dynamic biomarker of oxidative and metabolic stress, supporting its integration into broader biomarker panels for CKD risk stratification and management.

CONTRIBUTION OF AUTHORS

Research concept- Sudeep Jena, Subrat Pradhan
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Data analysis and interpretation- Rasmita Kumari Padhy
Literature search- Sudeep Jena, Shubhashree Priyadarshinee Singh
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Critical review- Rasmita Kumari Padhy
Article editing- Subrat Pradhan, Shubhashree Priyadarshinee Singh
Final approval- Rasmita Kumari Padhy

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