

Declining Antioxidant Defense Correlates with Albuminuric Injury in Chronic Kidney Disease

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Abstract

Background: Chronic kidney disease (CKD) is characterized by progressive loss of renal function and high cardiovascular risk. Microalbuminuria reflects glomerular and endothelial injury and is widely used for risk stratification. Oxidative stress has been implicated in CKD progression, yet the relationship between systemic antioxidant defenses and microalbuminuria across CKD stages requires clearer clinical characterization.

Objective: To evaluate stage-wise changes in antioxidant biomarkers and to determine their association with microalbuminuria among CKD patients.

Methods: This observational cross-sectional study included 60 CKD patients spanning stages 1–5. Participants were grouped as early CKD (stages 1–2), moderate CKD (stage 3), and advanced CKD (stages 4–5). Enzymatic antioxidants—superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx)—and total antioxidant capacity (TAC) were assessed. Microalbuminuria was measured using the urinary albumin–creatinine ratio (ACR). Stage-wise comparisons, correlation analysis, and multivariate linear regression were performed, adjusting for age, diabetes mellitus, and CKD stage.

Results: Antioxidant biomarkers showed a significant progressive decline with advancing CKD stage (all $p < 0.001$), while ACR increased markedly across stages ($p < 0.001$). TAC demonstrated the strongest inverse correlation with ACR ($r = -0.50$, $p < 0.001$), followed by GPx ($r = -0.48$, $p < 0.001$). In multivariate regression analysis, TAC ($\beta = -0.40$, $p < 0.001$) and GPx ($\beta = -0.35$, $p = 0.002$) remained independent negative predictors of microalbuminuria, whereas CKD stage ($\beta = +0.45$, $p < 0.001$) and diabetes mellitus ($\beta = +0.20$, $p = 0.01$) were positive predictors.

Conclusion: Declining antioxidant defense is independently associated with microalbuminuria in CKD, supporting oxidative imbalance as a mechanistic contributor to albuminuric renal injury.

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Introduction

Chronic kidney disease (CKD) is a progressive disorder marked by persistent abnormalities of kidney structure or function and is associated with substantial morbidity and mortality. Beyond progression to kidney failure, CKD substantially amplifies cardiovascular risk through intertwined metabolic, inflammatory, and vascular pathways. Early identification of modifiable mechanisms that contribute to renal injury remains central to improving long-term outcomes in CKD populations [1,2].

Microalbuminuria, typically assessed as the urinary albumin–creatinine ratio (ACR), is a clinically practical marker of glomerular barrier dysfunction

and systemic endothelial injury. Even modest elevations in urinary albumin excretion are linked to higher risk of CKD progression and cardiovascular events, making microalbuminuria both a prognostic indicator and a therapeutic target. Importantly, albuminuria is not only a consequence of declining filtration but also reflects dynamic processes including endothelial dysfunction, oxidative injury, inflammation, and altered intraglomerular hemodynamics [3–5].

Oxidative stress—defined as an imbalance between reactive oxygen species (ROS) generation and antioxidant defense—has emerged as a major biological pathway implicated in CKD

pathogenesis. In CKD, ROS production may increase due to chronic inflammation, mitochondrial dysfunction, activation of enzymatic oxidant systems, and accumulation of uremic toxins. Elevated oxidative stress can drive lipid peroxidation, protein modification, and DNA damage, ultimately contributing to renal cellular injury, tubulointerstitial fibrosis, and vascular dysfunction. These processes are relevant across CKD etiologies and may accelerate both renal decline and cardiovascular complications [6–8].

Endogenous antioxidant defenses help neutralize ROS and limit oxidative injury. Key enzymatic antioxidants include superoxide dismutase (SOD), which catalyzes dismutation of superoxide radicals; catalase, which decomposes hydrogen peroxide; and glutathione peroxidase (GPx), which reduces peroxides using glutathione-dependent mechanisms. In addition to these enzymatic pathways, total antioxidant capacity (TAC) provides a composite estimate of systemic antioxidant potential, reflecting both enzymatic and non-enzymatic contributors. A progressive impairment of antioxidant defenses may increase vulnerability to oxidative damage and thereby influence clinically measurable outcomes such as albuminuria [7–9].

Although oxidative stress is frequently discussed in relation to CKD progression, there remains a need for clinically grounded evidence describing how antioxidant markers behave across CKD stages and how strongly they relate to microalbuminuria when major confounders such as CKD stage and diabetes mellitus are accounted for. Clarifying these relationships is important for two reasons: first, it strengthens mechanistic understanding of albuminuric injury in CKD; and second, it informs whether antioxidant measures may have value in risk stratification or therapeutic targeting alongside established renoprotective approaches [9,10].

Accordingly, the present study evaluates stage-wise variation in antioxidant biomarkers (SOD, catalase, GPx, and TAC) and examines their association with microalbuminuria (ACR) in a CKD cohort spanning stages 1–5. In addition to correlation analysis, the study applies multivariate regression to determine whether antioxidant parameters independently predict microalbuminuria after adjustment for clinically relevant covariates.

Materials and Methods

Study Design

This investigation was conducted as an observational, cross-sectional study aimed at characterizing the relationship between systemic antioxidant defense and microalbuminuria in chronic kidney disease (CKD). The analytical strategy had two objectives: first, to examine stage-

wise differences in antioxidant biomarkers and urinary albumin excretion across the CKD spectrum; and second, to determine whether antioxidant markers remain independently associated with microalbuminuria after accounting for major clinical determinants of albuminuria, including CKD stage and diabetes mellitus.

Study Population and CKD Staging

A total of 60 patients with CKD were included, spanning CKD stages 1 through 5. To support clinically interpretable comparisons and trend assessment across disease severity, participants were grouped into three CKD categories: early CKD (Stages 1–2), moderate CKD (Stage 3), and advanced CKD (Stages 4–5). Baseline clinical profiling was performed for each participant and included age, sex, duration of CKD, presence of hypertension, presence of diabetes mellitus, and CKD stage distribution. These variables served dual purposes: (i) describing the cohort characteristics, and (ii) functioning as key covariates in adjusted analyses evaluating predictors of microalbuminuria.

Measurement of Antioxidant Biomarkers

Systemic antioxidant status was evaluated using a predefined biomarker panel representing both enzymatic and global antioxidant defense. The enzymatic components included superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), while overall non-enzymatic and combined antioxidant capacity was represented by total antioxidant capacity (TAC). Biomarker levels were quantified from blood-derived measurements and expressed in standard reporting units (U/mL for SOD, catalase, and GPx; mmol/L for TAC). These markers were selected to capture complementary antioxidant pathways and to enable assessment of progressive antioxidant depletion across CKD severity strata.

Assessment of Microalbuminuria

Microalbuminuria was assessed using the urinary albumin–creatinine ratio (ACR), expressed as mg/g creatinine. ACR was treated as a continuous outcome variable for statistical analyses, allowing evaluation of (i) differences in albumin excretion across CKD groups, and (ii) associations between albuminuria and antioxidant biomarkers. Stage-wise increases in ACR were interpreted as reflecting progressive glomerular and endothelial injury with worsening CKD severity, consistent with the study's objective of linking oxidative imbalance to albuminuric damage.

Statistical Analysis

Data were summarized using standard descriptive statistics, with continuous variables reported as mean \pm standard deviation and categorical

variables reported as proportions. Group-wise analyses were performed to compare antioxidant biomarkers and ACR across the three CKD severity categories (Stages 1–2 vs Stage 3 vs Stages 4–5), and statistical significance for stage-wise differences was evaluated using appropriate group comparison testing, with p-values reported accordingly. Associations between antioxidant biomarkers and microalbuminuria were quantified using correlation analysis, including estimation of correlation coefficients and corresponding significance values (p-values), with particular focus on TAC and GPx given their stronger inverse relationships with ACR. To identify independent predictors of microalbuminuria, a multivariate linear regression model was then constructed with ACR as the dependent variable, incorporating antioxidant parameters and adjusting for major clinical covariates explicitly included in the analysis—age, diabetes mellitus, and CKD stage. Regression results were expressed using standardized beta (β) coefficients and p-values, and conventional statistical significance criteria ($p < 0.05$) were applied.

Results

Baseline Demographic and Clinical Characteristics of the Study Population: A total of 60 patients with chronic kidney disease (CKD) across stages 1 to 5 were included in the analysis. The mean age of the study population was 50 ± 12 years, with a nearly equal gender distribution (52% males and 48% females). Hypertension was the most prevalent comorbidity, present in 76% of patients, followed by diabetes mellitus in 52%. The majority of participants (70%) were in CKD stages 3–5, indicating moderate to advanced renal dysfunction.

The mean duration of CKD was 4.5 ± 2.1 years, reflecting a cohort with established disease. These baseline characteristics demonstrate a representative CKD population with common metabolic and cardiovascular risk factors.

Table 1 summarizes the demographic and clinical characteristics of the study population.

Table 1: Baseline Demographic and Clinical Characteristics of CKD Patients

Variable	Value
Age (years)	50 ± 12
Male sex (%)	52
Female sex (%)	48
Hypertension (%)	76
Diabetes mellitus (%)	52
CKD stage ≥ 3 (%)	70
Duration of CKD (years)	4.5 ± 2.1

Antioxidant Biomarker Profile and Microalbuminuria Across CKD Stages:

A progressive and statistically significant decline in antioxidant biomarkers was observed with advancing CKD stage. Mean levels of superoxide dismutase (SOD) decreased from 14.2 ± 2.6 U/mL in early CKD (Stages 1–2) to 7.3 ± 1.9 U/mL in advanced CKD (Stages 4–5) ($p < 0.001$). Similarly, catalase, glutathione peroxidase (GPx), and total antioxidant capacity (TAC) showed marked reductions with disease progression (all $p < 0.001$).

In contrast, microalbuminuria increased significantly with worsening renal function. The mean urinary albumin–creatinine ratio (ACR) rose from 58 ± 21 mg/g in early CKD to 360 ± 110 mg/g in advanced stages ($p < 0.001$), indicating progressive glomerular and endothelial injury. These findings demonstrate a stage-dependent inverse relationship between antioxidant defense and albuminuria.

Stage-wise comparisons are presented in Table 2, while the overall trend of antioxidant decline across CKD stages is illustrated in Figure 1.

Table 2: Antioxidant Biomarkers and Microalbuminuria Across CKD Stages

Parameter	CKD Stages 1–2	CKD Stage 3	CKD Stages 4–5	p-value
SOD (U/mL)	14.2 ± 2.6	11.6 ± 2.1	7.3 ± 1.9	<0.001
Catalase (U/mL)	50.1 ± 7.6	40.3 ± 6.8	34.6 ± 5.7	<0.001
GPx (U/mL)	10.2 ± 1.7	8.4 ± 1.6	5.6 ± 1.2	<0.001
TAC (mmol/L)	1.30 ± 0.24	1.12 ± 0.21	0.74 ± 0.19	<0.001
ACR (mg/g creatinine)	58 ± 21	145 ± 48	360 ± 110	<0.001

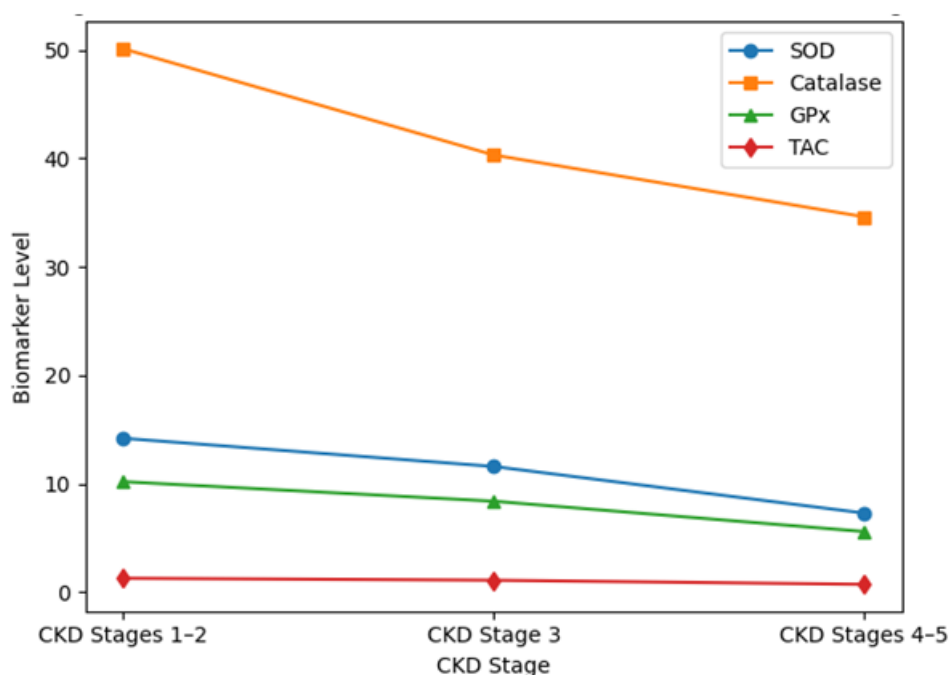


Figure 1: Progressive Decline in Antioxidant Biomarkers Across CKD Stages

Figure 1: Combined antioxidant biomarker trends across stages of chronic kidney disease. The line graph illustrates stage-wise changes in antioxidant defense markers. A consistent downward trend is observed for SOD, catalase, GPx, and TAC from early CKD (Stages 1–2) through moderate CKD (Stage 3) to advanced CKD (Stages 4–5). The steepest reductions are noted in GPx and TAC, indicating a marked impairment of enzymatic and non-enzymatic antioxidant defense with worsening renal function. These findings highlight increasing oxidative stress burden as CKD progresses.

Correlation Between Antioxidant Status and Microalbuminuria:

Correlation analysis

revealed significant inverse relationships between antioxidant biomarkers and microalbuminuria. Total antioxidant capacity (TAC) showed the strongest negative correlation with urinary ACR ($r = -0.50$, $p < 0.001$), followed by GPx ($r = -0.48$, $p < 0.001$). SOD and catalase also demonstrated statistically significant, though comparatively weaker, inverse correlations.

These findings indicate that lower antioxidant defense is associated with higher levels of microalbuminuria, suggesting a mechanistic link between oxidative stress and glomerular injury. The scatter plot illustrating the relationship between TAC and microalbuminuria is shown in Figure 2.

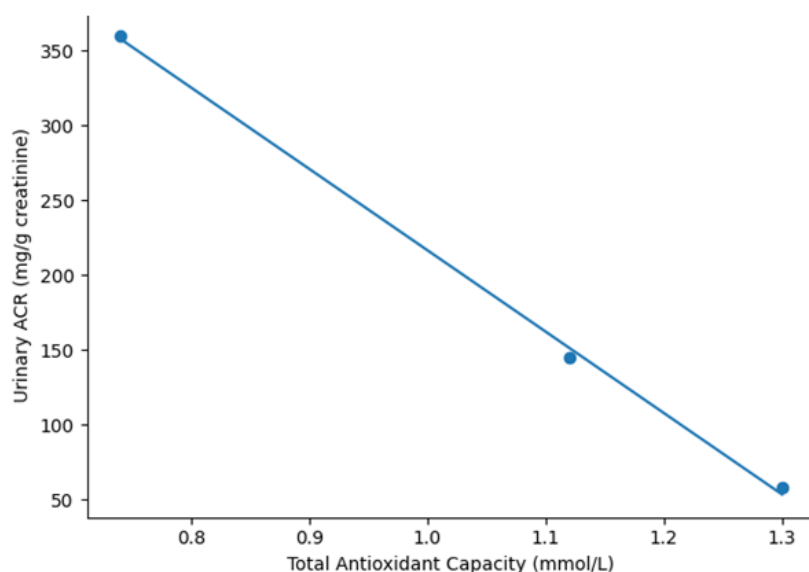


Figure 2: Inverse Correlation Between Total Antioxidant Capacity and Microalbuminuria

Figure 2: Inverse relationship between total antioxidant capacity and microalbuminuria. The scatter plot demonstrates a significant negative correlation between total antioxidant capacity (TAC) and urinary albumin–creatinine ratio (ACR). Patients with lower TAC levels exhibit markedly higher microalbuminuria. The fitted regression line emphasizes the strength and direction of this association, supporting the role of impaired antioxidant defense in the development of albuminuric renal injury

Multivariate Predictors of Microalbuminuria:

To identify independent predictors of microalbuminuria, a multivariate linear regression analysis was performed adjusting for age, diabetes mellitus, and CKD stage.

Total antioxidant capacity ($\beta = -0.40$, $p < 0.001$) and GPx ($\beta = -0.35$, $p = 0.002$) remained independent negative predictors of microalbuminuria. CKD stage was the strongest positive predictor ($\beta = +0.45$, $p < 0.001$), while diabetes mellitus also showed a significant association. Age did not independently predict microalbuminuria after adjustment.

The full regression model is presented in Table 3.

Multivariate regression analysis identified both antioxidant and clinical factors as independent predictors of microalbuminuria (table 3 Figure 3). Total antioxidant capacity and glutathione peroxidase emerged as the strongest negative predictors, whereas CKD stage and diabetes mellitus were significant positive predictors.

Table 3: Multivariate Regression Analysis for Predictors of Microalbuminuria

Variable	β Coefficient	p-value
Total Antioxidant Capacity	-0.40	<0.001
Glutathione Peroxidase	-0.35	0.002
CKD Stage	+0.45	<0.001
Diabetes mellitus	+0.20	0.01
Age	NS	0.10

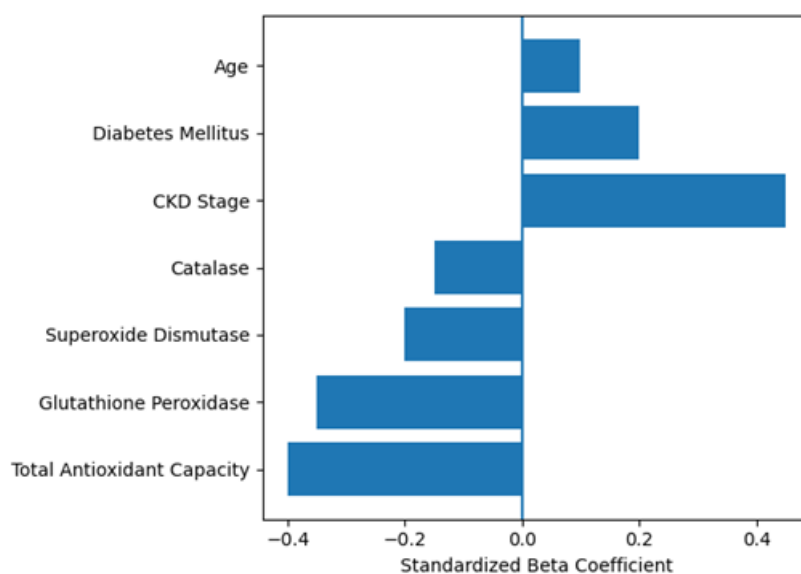


Figure 3: Multivariate regression analysis for predictors of microalbuminuria

The horizontal bar plot displays standardized beta coefficients derived from multivariate linear regression analysis assessing predictors of urinary microalbuminuria. Negative beta values indicate protective associations, while positive values indicate increased risk. Total antioxidant capacity and glutathione peroxidase show the strongest inverse associations with microalbuminuria, underscoring the protective role of antioxidant defense. In contrast, advancing CKD stage and diabetes mellitus demonstrate strong positive associations, reflecting disease severity and metabolic burden as key drivers of albuminuric

injury. Age shows a comparatively weaker and non-significant association after adjustment.

Discussion

This study demonstrates a consistent and clinically meaningful association between antioxidant depletion and increasing microalbuminuria across stages of chronic kidney disease (CKD). We observed a progressive decline in key antioxidant defenses (SOD, catalase, GPx, and total antioxidant capacity), alongside a marked rise in urinary albumin excretion with advancing CKD severity. The inverse correlations—strongest for total

antioxidant capacity and GPx—support the concept that oxidative stress is not only a bystander phenomenon in CKD but is mechanistically linked to albuminuric renal injury and disease progression [11–13].

The reduction in enzymatic antioxidants is biologically plausible in CKD. Persistent inflammation, accumulation of uremic toxins, mitochondrial dysfunction, and activation of NADPH oxidase pathways are known to increase reactive oxygen species (ROS) generation, overwhelming endogenous antioxidant systems [14]. As antioxidant reserves decline, ROS-mediated lipid peroxidation and protein oxidation can compromise glomerular and vascular integrity, contributing to endothelial dysfunction and enhanced albumin leakage across the filtration barrier [15]. Microalbuminuria in this context can be interpreted as an integrated marker of both glomerular capillary injury and systemic endothelial stress, which explains its strong prognostic relevance for CKD progression and cardiovascular risk [16].

Our multivariate regression findings strengthen the inference that antioxidant status has an independent relationship with microalbuminuria. Even after adjustment for CKD stage and diabetes mellitus, total antioxidant capacity and GPx remained significant predictors, suggesting that oxidative imbalance may exert effects beyond the degree of renal impairment alone [17]. This is particularly important because CKD stage is a dominant driver of albuminuria; demonstrating independent associations implies that antioxidant depletion may contribute directly to albuminuric injury, potentially offering a modifiable therapeutic target [18].

Diabetes mellitus emerged as a positive predictor of microalbuminuria, consistent with hyperglycemia-driven oxidative stress, advanced glycation end-products, and microvascular injury that accelerate renal endothelial dysfunction [19]. The stronger albuminuria signal in more advanced CKD stages likely reflects cumulative oxidative injury, loss of nephron mass, and worsening intraglomerular hemodynamics, reinforcing the value of microalbuminuria as a severity marker in CKD monitoring [20]. Clinically, these findings support incorporating oxidative stress and antioxidant profiling into CKD risk stratification research. While causality cannot be confirmed due to the cross-sectional design, the observed stage-wise patterns and independent associations provide a strong rationale for prospective studies and interventional trials evaluating antioxidant-targeted strategies as adjuncts to standard renoprotective therapy.

Conclusion

This study demonstrates a significant inverse relationship between antioxidant defense and microalbuminuria in chronic kidney disease. Antioxidant biomarkers (SOD, catalase, GPx, and total antioxidant capacity) declined progressively with advancing CKD stage, while urinary albumin excretion increased, indicating worsening glomerular and endothelial injury. Total antioxidant capacity and GPx remained independent predictors of microalbuminuria after adjustment for CKD stage and diabetes, supporting oxidative stress as a key mechanistic contributor to albuminuric renal damage. These findings justify prospective studies to evaluate antioxidant-focused strategies for improving CKD outcomes.

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