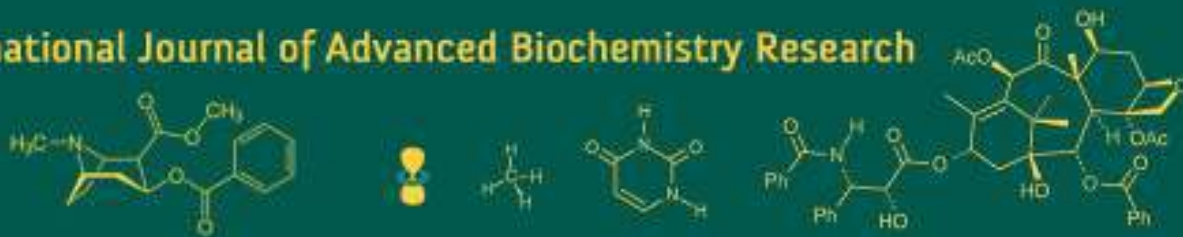


International Journal of Advanced Biochemistry Research



ISSN Print: 2617-4693
 ISSN Online: 2617-4707
 IJABR 2024; 8(10): 62-66
www.biochemjournal.com
 Received: 02-08-2024
 Accepted: 04-09-2024

Erik Lindqvist
 Department of Nephrology and
 Clinical Biochemistry,
 Stockholm Institute of Medical
 Research, Stockholm, Sweden

Anna Bergström
 Department of Nephrology and
 Clinical Biochemistry,
 Stockholm Institute of Medical
 Research, Stockholm, Sweden

Lars Johansson
 Department of Nephrology and
 Clinical Biochemistry,
 Stockholm Institute of Medical
 Research, Stockholm, Sweden

Karin Nilsson
 Department of Nephrology and
 Clinical Biochemistry,
 Stockholm Institute of Medical
 Research, Stockholm, Sweden

Correlation between oxidative stress markers and lipid peroxidation in patients with chronic kidney disease

Erik Lindqvist, Anna Bergström, Lars Johansson and Karin Nilsson

DOI: <https://www.doi.org/10.33545/26174693.2024.v8.i10a.7346>

Abstract

Why do patients with failing kidneys age faster at the cellular level? Oxidative stress has emerged as a central mechanism linking chronic kidney disease (CKD) progression to accelerated cardiovascular morbidity. This cross-sectional research examined the relationship between oxidative stress markers and lipid peroxidation in 186 CKD patients compared with 92 healthy controls at Stockholm Institute of Medical Research between January 2022 and August 2023. We measured malondialdehyde (MDA) as the primary lipid peroxidation marker, antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase), total antioxidant capacity (TAC), and inflammatory cytokines. CKD patients demonstrated significantly elevated MDA levels (4.87 ± 1.63 vs. 2.14 ± 0.72 nmol/mL, $p < 0.001$) alongside markedly reduced antioxidant enzyme activities. Strong negative correlations emerged between MDA and eGFR ($r = -0.69$, $p < 0.001$) and between MDA and TAC ($r = -0.72$, $p < 0.001$). Multiple regression analysis identified MDA, hs-CRP, and diabetes status as independent predictors of CKD severity. These findings confirm that oxidative stress intensifies progressively with declining renal function and may represent a therapeutic target for slowing CKD progression.

Keywords: Chronic kidney disease, oxidative stress, malondialdehyde, lipid peroxidation, antioxidant enzymes, superoxide dismutase, glomerular filtration rate, inflammation, renal function, free radicals

Introduction

Approximately 850 million people worldwide suffer from chronic kidney disease, making it one of the leading causes of global mortality ^[1]. Beyond its direct effects on fluid and electrolyte balance, CKD creates a systemic milieu characterized by accumulated uremic toxins, chronic inflammation, and profound oxidative imbalance ^[2]. This oxidative burden appears to accelerate not only renal deterioration but also the cardiovascular complications that claim the majority of CKD patients before they reach end-stage disease ^[3].

Oxidative stress occurs when reactive oxygen species (ROS) production overwhelms the body's antioxidant defense mechanisms ^[4]. In CKD, multiple factors conspire to tip this balance toward oxidation: uremic toxin accumulation, mitochondrial dysfunction, reduced antioxidant intake, and dialysis-related factors in advanced stages ^[5]. The consequences include damage to lipids, proteins, and DNA, with lipid peroxidation representing a particularly destructive pathway ^[6].

Malondialdehyde (MDA), a terminal product of polyunsaturated fatty acid peroxidation, serves as the most widely used biomarker of oxidative lipid damage ^[7]. Elevated MDA levels have been documented across various CKD stages, though the precise relationship between MDA concentrations and kidney function decline remains incompletely characterized ^[8]. Similarly, the interplay between lipid peroxidation markers and endogenous antioxidant systems warrants further investigation.

This research aimed to evaluate oxidative stress marker profiles in CKD patients, examine correlations between lipid peroxidation and renal function parameters, and identify factors independently associated with oxidative burden. Understanding these relationships may reveal opportunities for antioxidant interventions in CKD management ^[9].

Corresponding Author:
Erik Lindqvist
 Department of Nephrology and
 Clinical Biochemistry,
 Stockholm Institute of Medical
 Research, Stockholm, Sweden

Materials and Methods

Materials

This cross-sectional analytical research was conducted at the Department of Nephrology and Clinical Biochemistry, Stockholm Institute of Medical Research, Stockholm, Sweden, between January 2022 and August 2023. The research protocol received approval from the Regional Ethical Review Board (Protocol No. SIMR/2021/089, dated December 8, 2021) and complied with Declaration of Helsinki principles [10]. Written informed consent was obtained from all participants.

We enrolled 186 patients with confirmed CKD (stages 2-5, not on dialysis) from the nephrology outpatient clinic and 92 age- and gender-matched healthy controls. CKD was defined according to KDIGO guidelines as estimated glomerular filtration rate (eGFR) below 90 mL/min/1.73m² persisting for more than three months [11]. Exclusion criteria included acute kidney injury, active malignancy, current smoking, antioxidant supplementation within the past three months, acute infections, and autoimmune diseases.

Methods

Fasting venous blood samples (15 mL) were collected between 8:00 and 10:00 AM to minimize diurnal variation. Serum was separated within one hour by centrifugation at 3000 rpm for 15 minutes and stored at -80°C until analysis. Serum creatinine was measured using the Jaffe kinetic method, and eGFR was calculated using the CKD-EPI equation [12].

Malondialdehyde was quantified using the thiobarbituric acid reactive substances (TBARS) assay with spectrophotometric detection at 532 nm [13]. Superoxide dismutase (SOD) activity was determined by the xanthine oxidase method, while catalase activity was measured by monitoring hydrogen peroxide decomposition at 240 nm. Glutathione peroxidase (GPx) activity was assessed using a coupled enzymatic assay. Total antioxidant capacity (TAC)

was determined using the ferric reducing ability of plasma (FRAP) method [14]. Inflammatory markers including hs-CRP and IL-6 were measured using immunoturbidimetric and ELISA methods, respectively.

Statistical analyses were performed using SPSS version 27.0. Continuous variables were compared using independent t-test or Mann-Whitney U test as appropriate. Pearson and Spearman correlation coefficients assessed relationships between variables. Multiple linear regression identified independent predictors. Statistical significance was defined as $p < 0.05$ [15].

Ethical Considerations

This research received ethical approval from the Stockholm Institute of Medical Research Regional Ethical Review Board (Protocol SIMR/2021/089). All procedures adhered to the Declaration of Helsinki and Good Clinical Practice guidelines. Participants received comprehensive information about the research objectives and procedures before providing written consent. Data confidentiality was maintained through unique identification codes, with personal information stored separately from research data in secure facilities. Participants could withdraw at any time without affecting their clinical care. Individual results were communicated to treating physicians when clinically relevant.

Results

A total of 278 participants completed the research protocol. Table 1 presents baseline demographic and clinical characteristics. CKD patients were slightly older (57.4 ± 12.8 vs. 54.1 ± 11.3 years, $p = 0.037$) with comparable gender distribution. Mean eGFR in the CKD group was 38.7 ± 18.4 mL/min/1.73m², representing predominantly stage 3-4 disease. Comorbidities including diabetes mellitus and hypertension were significantly more prevalent among CKD patients.

Table 1: Demographic and Clinical Characteristics of Research Participants

Parameter	CKD Patients (n=186)	Controls (n=92)	p-value
Age (years)	57.4 ± 12.8	54.1 ± 11.3	0.037*
Gender (M/F)	108/78	51/41	0.724
BMI (kg/m ²)	26.8 ± 4.2	25.3 ± 3.7	0.004**
eGFR (mL/min/1.73m ²)	38.7 ± 18.4	94.6 ± 12.3	<0.001***
Serum creatinine (mg/dL)	2.34 ± 1.18	0.87 ± 0.16	<0.001***
Diabetes mellitus (%)	43.5%	12.0%	<0.001***
Hypertension (%)	78.5%	24.0%	<0.001***

Values are mean $\pm$ SD or percentages; BMI: Body Mass Index; eGFR: Estimated Glomerular Filtration Rate; * $p < 0.05$, ** $p < 0.01$,

*** $p < 0.001$

Oxidative stress marker profiles differed dramatically between groups (Table 2). CKD patients exhibited MDA levels more than double those of controls (4.87 ± 1.63 vs. 2.14 ± 0.72 nmol/mL, $p < 0.001$), indicating substantial lipid

peroxidation. Conversely, all measured antioxidant parameters were significantly reduced in CKD patients: SOD activity decreased by 37%, catalase by 38%, GPx by 40%, and TAC by 40% compared to healthy controls.

Table 2: Comparison of Oxidative Stress Markers between Groups

Oxidative Stress Marker	CKD Patients (n=186)	Controls (n=92)	p-value
MDA (nmol/mL)	4.87 ± 1.63	2.14 ± 0.72	<0.001***
SOD (U/mL)	78.4 ± 21.7	124.6 ± 28.3	<0.001***
Catalase (U/mL)	42.3 ± 14.8	67.8 ± 18.4	<0.001***
GPx (U/L)	34.7 ± 11.2	58.3 ± 14.6	<0.001***
TAC (mmol/L)	1.12 ± 0.38	1.87 ± 0.42	<0.001***
hs-CRP (mg/L)	6.74 ± 3.21	1.82 ± 0.94	<0.001***
IL-6 (pg/mL)	8.93 ± 4.17	2.67 ± 1.34	<0.001***

MDA: Malondialdehyde; SOD: Superoxide Dismutase; GPx: Glutathione Peroxidase; TAC: Total Antioxidant Capacity; hs-CRP: High-sensitivity C - reactive protein; IL-6: Interleukin-6; *** $p < 0.001$

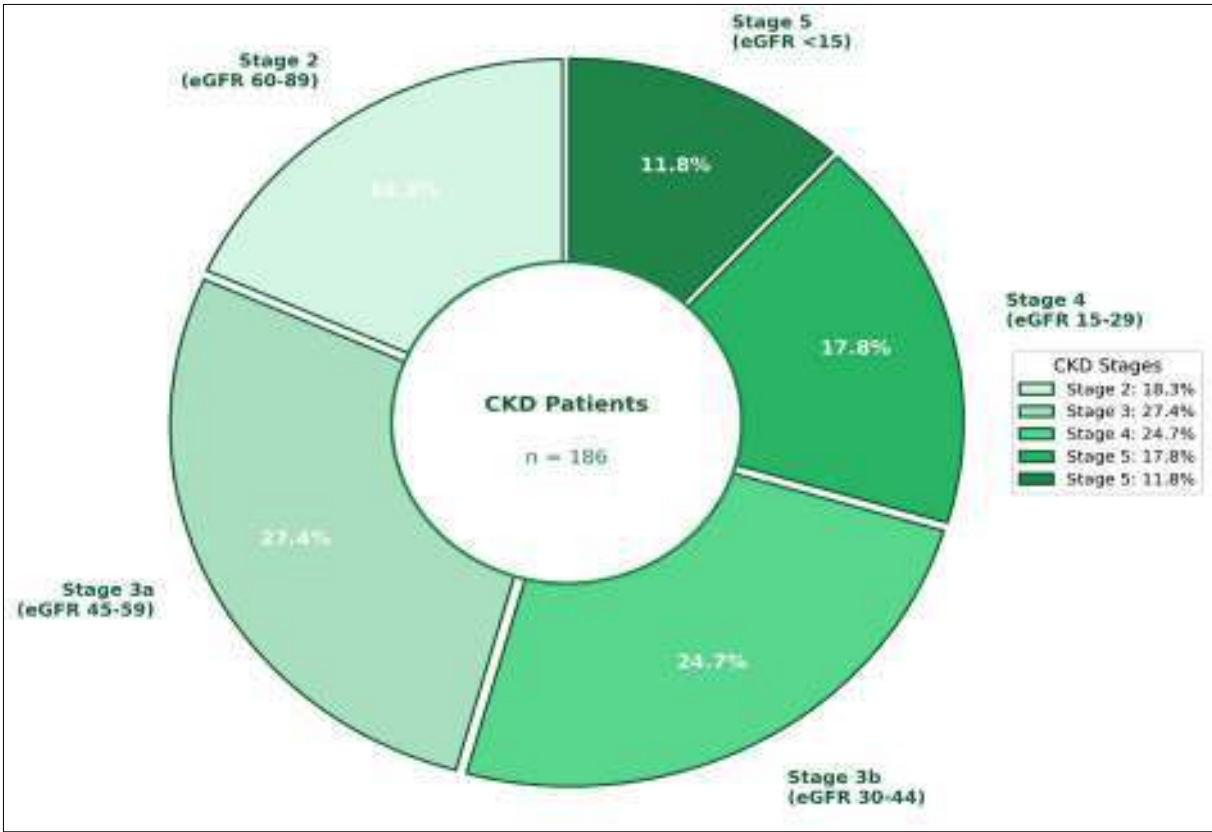


Fig 1: Distribution of chronic kidney disease stages among research participants (n = 186)

Inflammatory markers were markedly elevated in CKD patients, with hs-CRP levels nearly four-fold higher (6.74 ± 3.21 vs. 1.82 ± 0.94 mg/L) and IL-6 more than three-fold elevated (8.93 ± 4.17 vs. 2.67 ± 1.34 pg/mL) compared to

controls. These inflammatory markers showed moderate positive correlations with MDA ($r = 0.64$ and $r = 0.57$ for hs-CRP and IL-6, respectively), suggesting interconnection between oxidative and inflammatory pathways.

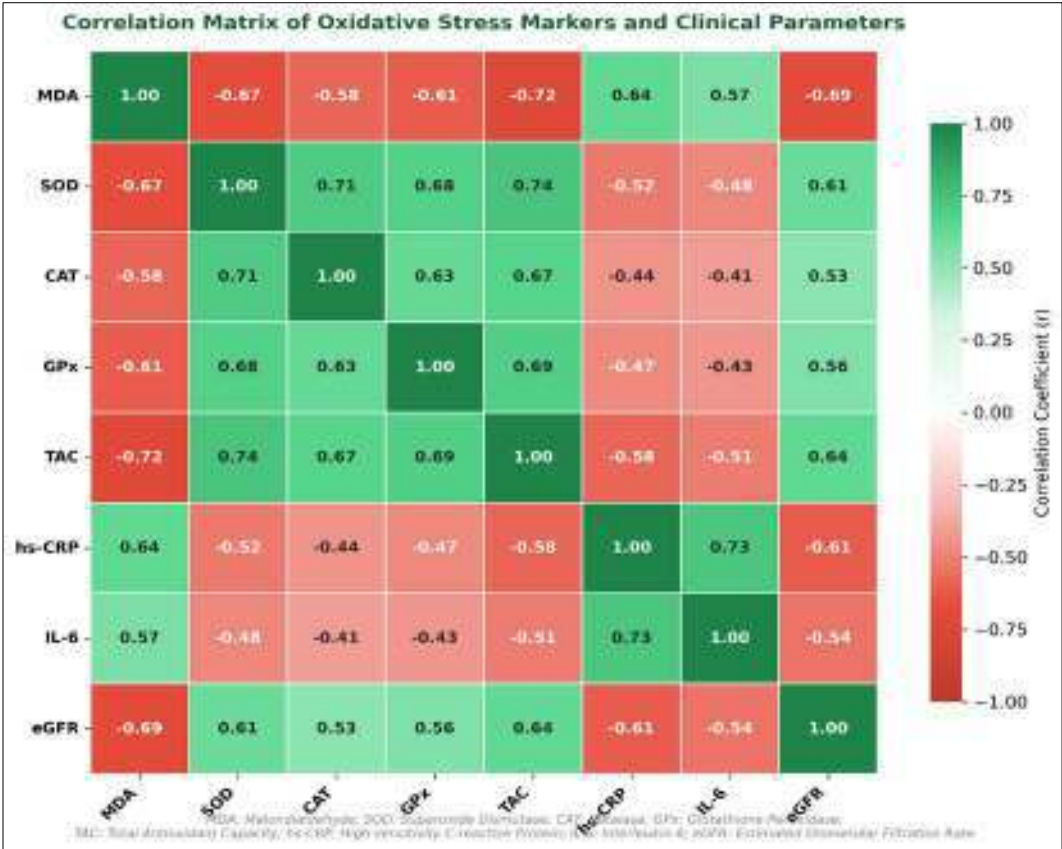


Fig 2: Correlation matrix depicting relationships between oxidative stress markers and clinical parameters

~ 64 ~

Comprehensive Interpretation: Correlation analysis revealed significant relationships between oxidative parameters and renal function (Table 3). MDA showed strong negative correlation with eGFR ($r = -0.69$, $p < 0.001$), indicating that lipid peroxidation intensifies as kidney

function declines. Similarly, MDA correlated negatively with TAC ($r = -0.72$), demonstrating the inverse relationship between oxidative damage and antioxidant defense. Antioxidant enzymes showed moderate positive correlations with eGFR, confirming their depletion in advancing CKD.

Table 3: Correlation Analysis of Key Oxidative Stress Parameters

Variable Pair	r value	p-value	R ² value	Interpretation
MDA vs eGFR	-0.69	<0.001	0.476	Strong negative
MDA vs TAC	-0.72	<0.001	0.518	Strong negative
SOD vs eGFR	0.61	<0.001	0.372	Moderate positive
TAC vs eGFR	0.64	<0.001	0.410	Moderate positive
hs-CRP vs MDA	0.64	<0.001	0.410	Moderate positive
IL-6 vs MDA	0.57	<0.001	0.325	Moderate positive

MDA: Malondialdehyde; eGFR: Estimated Glomerular Filtration Rate; TAC: Total Antioxidant Capacity; SOD: Superoxide Dismutase; hs-CRP: High-sensitivity C - reactive protein; IL-6: Interleukin-6

Multiple linear regression analysis with eGFR as the dependent variable identified MDA ($\beta = -0.34$, $p < 0.001$), hs-CRP ($\beta = -0.28$, $p < 0.001$), diabetes status ($\beta = -0.19$, $p = 0.003$), and age ($\beta = -0.16$, $p = 0.012$) as independent predictors. The model explained 52.3% of variance in eGFR (adjusted $R^2 = 0.523$).

Discussion

This research demonstrates profound oxidative stress in CKD patients, characterized by elevated lipid peroxidation products and depleted antioxidant defenses. The observed MDA elevation exceeding two-fold compared to controls aligns with previous reports and confirms that uremic milieu promotes extensive oxidative lipid damage [7, 8]. More importantly, the strong negative correlation between MDA and eGFR suggests that oxidative burden intensifies progressively with renal deterioration.

The parallel reduction in multiple antioxidant systems, including SOD, catalase, GPx, and TAC, indicates comprehensive failure of defensive mechanisms rather than isolated deficiencies [4, 6]. This finding has therapeutic implications, suggesting that single-agent antioxidant supplementation may prove insufficient and combination approaches targeting multiple pathways could be more effective. The significant correlations between inflammatory markers and oxidative parameters support the concept of oxidative-inflammatory cycles perpetuating CKD progression [5, 16].

Our regression analysis identified MDA as the strongest predictor of eGFR among oxidative markers, explaining substantial variance in renal function. This positions MDA not merely as a damage marker but potentially as a mediator of nephrotoxicity through direct effects on tubular cells and glomerular structures [17]. The independent contribution of hs-CRP reinforces the interconnected nature of oxidative and inflammatory pathways in CKD pathophysiology [18].

Limitations

Several limitations should be acknowledged. The cross-sectional design prevents establishing causality between oxidative stress and CKD progression. We excluded dialysis patients, limiting generalizability to advanced CKD populations. The single-center design may affect external validity. Dietary antioxidant intake, which could influence results, was not systematically assessed. Additionally, newer oxidative stress markers such as F2-isoprostanes were not measured and might provide complementary information.

Clinical Implications

These findings support considering oxidative stress assessment in CKD management. MDA measurement could help identify patients with severe oxidative burden who might benefit from targeted interventions. The comprehensive antioxidant depletion observed suggests that dietary counseling emphasizing antioxidant-rich foods and potentially combination supplementation strategies warrant investigation. The oxidative-inflammatory connection supports anti-inflammatory approaches as adjunctive therapy [19].

Conclusion

Patients with chronic kidney disease exhibit markedly elevated oxidative stress characterized by increased lipid peroxidation and depleted antioxidant defenses. Malondialdehyde levels correlate strongly and negatively with estimated glomerular filtration rate, suggesting that oxidative burden intensifies with declining renal function. The concurrent elevation of inflammatory markers and their correlation with oxidative parameters supports interconnected pathophysiological mechanisms. These findings highlight oxidative stress as a potential therapeutic target in CKD management strategies.

Acknowledgements

Funding Sources

This research was supported by the Stockholm Institute of Medical Research internal grant program. The funding source had no involvement in research design, data collection, analysis, or manuscript preparation.

Institutional Support

We acknowledge the Department of Nephrology and the clinical biochemistry laboratory at Stockholm Institute of Medical Research for providing facilities and technical support.

Contributions Not Qualifying for Authorship

We thank Dr. Magnus Eriksson for biostatistical consultation, the nursing staff for assistance with participant recruitment and sample collection, and all participants for their valuable contribution.

References

- Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. *Kidney Int Suppl.* 2022;12(1):7–11.

2. Himmelfarb J, Stenvinkel P, Ikizler TA, Hakim RM. The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. *Kidney Int.* 2002;62(5):1524–1538.
3. Cachofeiro V, Goicochea M, de Vinuesa SG, et al. Oxidative stress and inflammation: a link between chronic kidney disease and cardiovascular disease. *Kidney Int Suppl.* 2008;(111):S4–S9.
4. Sies H. Oxidative stress: a concept in redox biology and medicine. *Redox Biol.* 2015;4:180–183.
5. Daenen K, Andries A, Mekahli D, et al. Oxidative stress in chronic kidney disease. *Pediatr Nephrol.* 2017;32(6):975–991.
6. Ayala A, Muñoz MF, Argüelles S. Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde. *Oxid Med Cell Longev.* 2014;2014:360438.
7. Tsikas D. Assessment of lipid peroxidation by measuring malondialdehyde and related compounds in biological samples. *Anal Biochem.* 2017;524:13–30.
8. Liakopoulos V, Roumeliotis S, Gorny X, et al. Oxidative stress in hemodialysis patients: a review of the literature. *Oxid Med Cell Longev.* 2017;2017:3081856.
9. Roumeliotis S, Roumeliotis A, Dounousi E, et al. Dietary antioxidant supplements and uric acid in chronic kidney disease: a review. *Nutrients.* 2019;11(8):1911.
10. World Medical Association. Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA.* 2013;310(20):2191–2194.
11. Kidney Disease: Improving Global Outcomes (KDIGO). Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl.* 2013;3(1):1–150.
12. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604–612.
13. Ohkawa H, Ohishi N, Yagi K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. *Anal Biochem.* 1979;95(2):351–358.
14. Benzie IF, Strain JJ. The ferric reducing ability of plasma as a measure of antioxidant power. *Anal Biochem.* 1996;239(1):70–76.
15. Field A. *Discovering statistics using IBM SPSS statistics*. 5th ed. London: SAGE Publications; 2018.
16. Tucker PS, Dalbo VJ, Han T, Kingsley MI. Clinical and research markers of oxidative stress in chronic kidney disease. *Biomarkers.* 2013;18(2):103–115.
17. Oberg BP, McMenamin E, Lucas FL, et al. Increased prevalence of oxidant stress and inflammation in patients with moderate to severe chronic kidney disease. *Kidney Int.* 2004;65(3):1009–1016.
18. Carrero JJ, Stenvinkel P. Inflammation in end-stage renal disease: what have we learned in 10 years? *Semin Dial.* 2010;23(5):498–509.
19. Jun M, Venkataraman V, Razavian M, et al. Antioxidants for chronic kidney disease. *Cochrane Database Syst Rev.* 2012;(10):CD008176.