Review article

UDC: 616.61:577.1
doi:10.5633/amm.2022.0207

IMPLICATIONS OF OXIDATIVE STRESS IN END-STAGE KIDNEY DISEASE PATIENTS: A REVIEW OF CAUSATIVE MECHANISMS, CURRENT CONCEPTS

Vassilios Liakopoulos[1,2], Garyfallia Varouktsi[1,2], Ariti Tsinari[1,2], Andrej Veljković[3], Gordana Lazarević[4,5], Zoran Perišić[4,5], Jovan Hadži-Djokić[6], Gordana Kocić[3], Stefanos Roumeliotis[1,2]

Oxidative stress (OS), termed as the imbalance between antioxidants and pro-oxidants in favor of the latter, is highly prevalent in chronic kidney disease (CKD) even at early stages and is gradually increased, in parallel to deterioration of kidney function. In end-stage kidney disease (ESKD), OS is further aggravated and associated with various adverse outcomes, including atherosclerosis and cardiovascular disease. In this review, we aim to present the clinical implications of OS, the pathogenetic causative mechanisms and the potential therapeutic interventions in both hemodialysis and peritoneal dialysis patients.

Acta Medica Medianae 2022;61(2):53-59.

Key words: *cardiovascular disease, chronic kidney disease, end-stage kidney disease, hemodialysis, oxidative stress, peritoneal dialysis, vitamin C, vitamin E*

[1]Division of Nephrology and Hypertension, 1st Department of Internal Medicine, AHEPA Hospital, Thessaloniki, Greece
[2]Aristotle University of Thessaloniki, School of Medicine, Thessaloniki, Greece
[3]University of Niš, Faculty of Medicine, Department of Biochemistry, Niš, Serbia
[4]University Clinical Center Niš, Division of Cardiology, Niš, Serbia
[5]University of Niš, Faculty of Medicine, Niš, Serbia
[6]Serbian Academy of Sciences and Arts, Belgrade, Serbia

Contact: Vassilios Liakopoulos
1 St. Kyriakidi Street, 54636 Thessaloniki, Greece
E-mail: vliak@auth.gr

Introduction

Chronic kidney disease (CKD) is a major health problem worldwide, affecting 11-13% of the global population, a percentage that is expected to rise dramatically in the next decade (1). Cardiovascular (CV) disease is highly prevalent and remains the major cause of mortality in these patients. Even at early CKD stages 1-2, patients are at risk for sudden CV death and as the disease progresses to end stage kidney disease (ESKD), this risk is further exacerbated (2). Thus, when compared to the general population and after adjustment for age, diabetes and hypertension, ESKD patients have a 2-fold increased risk for CV death (3, 4). This is why the expected remaining lifespan of ESKD patients undergoing maintenance hemodialysis (HD) is 8 years for patients between 40 and 44 years old and under 4.5 years for 60-64 years old (4). Although the Framingham traditional CV risk factors such as age, gender, obesity, hypertension, smoking, diabetes, dyslipidemia, sedentary lifestyle and heart failure are over-represented, they cannot solely explain the heavy CV burden seen in these patients. During the past decades, novel-uremia-specific non-traditional risk factors have emerged, including anemia, inflammation, oxidative stress (OS), endothelial dysfunction, hypoalbuminemia, malnutrition and abnormal calcium metabolism. These novel risk factors might explain the CV burden of ESKD patients and represent potential treatment targets. OS, a novel non-traditional risk factor, is a common pathogenetic mechanism underlying both the occurrence and progression of CV disease in ESKD patients.

Definition and markers of OS in CKD and ESKD

Every molecule that is missing an electron is defined as "pro-oxidant", whereas an agent that donates electrons to other molecules is termed "anti-oxidant". OS is the disturbance of balance between pro-oxidants and anti-oxidant agents, in favor of pro-oxidants. Pro-oxidant molecules, such as nitric oxide (NO) and reactive oxygen species (ROS) are highly reactive agents and in order to become stabilized, they "steal" an electron from adjacent biomolecules (including proteins, lipids, nucleic acids and carbohydrates) causing structural and functional

modification and subsequent oxidative injury in the cells and tissues. In an attempt to counteract the injury caused by free radicals, endogenous antioxidants are generated to de-activate ROS. Since free radicals are chemically unstable molecules, their measurement in plasma or serum is very difficult to be performed. Therefore, the serum or plasma levels of oxidative molecules and endogenous antioxidants might serve as markers of OS status. Markers of protein oxidation include thiols, carbonyls, homocysteine, myeloperoxidase (MPO), oxidized albumin asymmetric dimethylarginine (ADMA) and advanced oxidation proteins products (AOPPs); markers of nucleic acid oxidation include 8-hydroxy deoxyguanosine and 8-Oxo-2-deoxyguanosine; markers of lipid peroxidation include malondialdehyde (MDA), oxidized low density lipoprotein (ox-LDL), F2-isoprostanes, thiobarbituric acid reactive substances (TBARS), lipoperoxides, advanced lipid oxidation products and advanced glycation end-products (AGEs) are the main marker of carbohydrate oxidation. On the other hand, enzymatic antioxidant markers include catalase (CAT), superoxide dismutase (SOD), glutathione transferase, glutathione peroxidase and total antioxidant capacity (TAC), whereas non-enzymatic antioxidant markers include glutathione, reduced glutathione, uric acid (5), albumin, transferrin and ferritin, zinc, copper and selenium, N-acetylcysteine (NAC), vitamins B, C, D, E, A-lipoic acid, flavonoids, polyphenols, L-carnitine, Q-enzyme 10, green tea, curcumin, statins and omega-3 fatty acids (6).

In early CKD, OS is present and increases gradually with kidney function impairment to ESKD (7). This could be attributed to various reasons. First, due to the uremic environment, several molecular pathways - such as the mitochondrial respiratory chain reaction, the activity of dinucleotide phosphate oxidase (NADPH) and NO synthase- are severely de-arranged and lead to overproduction of pro-oxidants (8). Second, due to inadequate kidney clearance, these pro-oxidants accumulate in the circulation and third, the naturally occurring antioxidants present reduced activity and decreased concentrations in plasma and serum (9). Patients even at very early CKD stages have higher OS status compared to healthy subjects (10), whereas in a cohort of 87 patients at CKD stages 1-4, it was shown that F2-isoprostanes increased and TAC decreased progressively, across the stages of the disease (11).

Compared to pre-dialysis CKD, in ESKD, OS is further exacerbated and results in oxidative damage of the kidney (renal ischemia, glomerular damage and tubular apoptosis), upregulation and activation of systemic inflammatory cytokines, such as c-reactive protein (CRP), interleukin-6 and -10 (IL-6, IL-10), tumor necrosis factor-alpha (TNF-α) and subsequently endothelial dysfunction and atherosclerosis (12, 13). "Although dialysis per se triggers all the aforementioned molecular pathways, it was not clear whether the main culprit for the increased OS seen in ESKD patients is dialysis procedure or kidney damage." Data from studies where ESKD patients undergoing HD were subjected to kidney transplantation and kidney function was restored, showed that within 2 months post-transplantation all markers of OS and inflammation were normalized (14).

OS in ESKD patients undergoing maintenance HD

Compared to pre-dialysis CKD patients and healthy subjects, ESKD patients undergoing maintenance HD present significantly increased OS status for various reasons. First, the dietary instructions in ESKD to avoid consumption of fruits and vegetables (that are rich in potassium) and the possible malnutrition that usually accompanies these patients might result in decreased intake of important antioxidants, such as vitamins B, C, D and E (15, 16). Second, various comorbidities that are common among ESKD patients, including hypertension, anemia, advanced age, dyslipidemia, diabetes mellitus, and atherosclerosis trigger generation of free radicals (17). Third, in ESKD, the endogenous antioxidant defense systems are significantly impaired (18) and four, the chronic micro-inflammation status that usually accompanies HD, might also contribute to generation of pro-oxidants. Finally, the HD procedure per se triggers OS through several pathogenetic mechanisms.

Due to the contact of blood with the bioincompatible, artificial membranes and dialysate, within 15 minutes after initiation of dialysis, ROS are abruptly generated and released to circulation by white blood cells (19, 20). It is estimated that after every 4 hour HD session ROS levels are fourteen times higher than before the session (21), whereas certain amounts of antioxidant vitamins and trace elements are lost (22, 23). Since the main mechanism underlying the oxidative burst of polymorphonuclear white blood cells is the bioincompatible dialyzer membranes, several investigators aimed to study whether the development of new, more biocompatible membranes might ameliorate OS and benefit HD patients. Several studies reported that compared to the older, cuprophane membranes, newer, more biocompatible polysulfone membranes were associated with decreased lipid peroxidation status (24, 25), reduced generation of ROS (26, 27) and increased levels of the antioxidants CAT (25) and vitamin E (28). Similarly, compared to cuprophane, regenerated cellulose membranes were related with reduced production of free radicals (29). Of note, no study has assessed the effect of these newer, more biocompatible membranes with clinical hard CV outcomes. Moreover, although the newer, synthetic, more biocompatible membranes are better compared to the old, cuprophane membranes, these membranes still trigger activation of pro-oxidants and therefore their designation as "biocompatible" is a debatable term.

Another HD-related factor implicated in the pathogenesis of OS is the use of anticoagulation; heparin is suggested to trigger oxidation of fatty acids (30), whereas citrate anticoagulation might be of benefit, regarding lipid peroxidation status (31). In a comparative study, Gritters et al. (32) examined the white blood cells' oxidative burst during HD session using citrate or classical heparin or low molecule weight dalteparin. The authors found that

in HD with classical or low molecular weight heparin, ROS were abruptly increased within the first ten times of HD session, whereas HD with citrate was associated with significantly decreased markers of lipid peroxidation, such as MPO and ox-LDL.

Ultrapure dialysate is fundamental in HD. Even the slightest concentration of bacterial toxins in the dialysate compromises the biocompatibility of HD session and triggers the activity of pro-oxidants (33, 34). On the other hand, HD treatment with ultrapure dialysate is suggested to ameliorate both inflammation and OS biomarkers and improve anemia status (35-37). A large meta-analysis of 31 studies including 1580 HD patients clearly showed that HD with ultrapure dialysate successfully suppressed plasma levels of ox-LDL, MPO, IL-6 and MPO (38).

Another factor related with increased OS in HD is problematic or failed HD vascular access, such as the use of misplaced central venous catheters and malfunctioning arteriovenous fistulae or grafts (39, 40). Weiss et al. (39), reported that in arteriovenous fistulae and grafts that were removed due to thrombotic episodes or aneurysm formation, markers of lipid, carbohydrate and protein oxidation were overexpressed. Of note, the majority of these tissues did not present inflammation.

Accumulating evidence suggests that anemia triggers OS in HD patients (41-43), whereas its correction significantly abrogates the oxidation process (42, 44, 45). Besides erythropoietin stimulating agents, the treatment of anemia in HD also includes intravenous iron infusion. Intravenous infusion of 100 mg iron sucrose triggered an abrupt formation of MDA 30 minutes after the initiation of the process in pre-dialysis anemic CKD patients (46, 47), and generation of MDA and OS-derived DNA damage in HD patients (48-50). To explore the degree of OS caused by intravenous iron administration, Tovbin et al. (51), infused 100 mg of iron saccharate for 3.5 hours in 19 HD patients and found a 37% increase in markers of protein oxidation after the end of HD session. The duration of iron infusion influenced the oxidative response triggered. Rapid or bolus intravenous administration caused an abrupt increase in free radicals, probably due to transient oversaturation of transferrin and iron overload (52, 53). Slow intravenous infusion of iron agents is suggested in HD patients, to give time to naturally occurring antioxidant defense mechanisms to counteract and neutralize the gradual generation of free radicals (54, 55).

OS in ESKD patients on peritoneal dialysis

Not all ESKD patients undergo HD treatment; it is estimated that nearly 196,000 ESKD patients worldwide, representing 12–15% of the dialysis population choose peritoneal dialysis (PD) as renal replacement therapy (RRT) (56). Although in HD, OS has been thoroughly investigated, in PD, the data remain limited. Compared to pre-dialysis CKD and ESKD patients, OS is higher in PD patients; however, the OS in PD is triggered without using bioincompatible membranes, dialysate, malfunctioning vascular access or heparin. The main culprit that is responsible for the OS in PD patients is the biocompatibility of PD solutions, including the high glucose concentration, the acidic pH, the lactate buffer and the increased osmolarity (57). Peritoneal mesothelial cells exposed to conventional PD solutions die from apoptosis within 40 minutes from their exposure (58). PD solutions include water, high glucose, lactate buffer and various electrolytes. When these solutions are heated, before entering the peritoneal cavity, AGEs and glucose degradation products (GDPs) are formatted (59). Exposure of peritoneal mesothelial and endothelial cells to the high glucose and the AGEs of the PD solution activate several molecular pathways similar to those underlying the pathogenesis of diabetic CKD, including the polyol pathway, glucose-oxidation and diacylglycerol pathway and activation of protein kinase C (60). Subsequently, growth factors (such as vascular endothelial growth factor), inflammatory (such as IL-6, IL-1, IL-10 and CRP) and OS markers are activated in the peritoneal cavity. Chronic exposure of the peritoneal cavity to these factors results in peritoneal fibrosis and thickening, angiogenesis, vasculopathy, progressive transformation of the peritoneal membrane and systemic OS and inflammation (60).

Therapeutic options to ameliorate OS in HD and PD

To counteract the deleterious effects of OS in HD, several lifestyle modifications have been proposed, including cessation of smoking, optimal management of blood pressure, lipids and glycemic control. Other interventions include use of a functional vascular access, correction of anemia status, slow intravenous infusion of iron and use of biocompatible dialyzers and ultrapure dialysate. Similarly, in PD, a multitargeted approach is needed, including limited salt and water intake, strict glycemic control and use of newer, more biocompatible PD solutions with low glucose, low GDPs, bicarbonate lactate and neutral pH.

Moreover, several investigators suggested that supplementation with exogenous antioxidants, including vitamin C, vitamin E and NAC could benefit EKSD patients. It has been shown that in every dialysis session about 66 mg of vitamin C are lost through the dialyzer, whereas vitamin C depletion is highly prevalent in HD patients (61). Several studies examined whether oral or intravenous supplementation of vitamin C might ameliorate OS in HD patients and produced contraindicatory results (62-66). Moreover, these studies have major limitations, including small sample size and wide diversity on follow-up time and doses used. A recent meta-analysis of 11 randomized controlled trials and 491 HD patients (67) reported that vitamin E supplementation improved endothelial dysfunction, and significantly decreased CRP and MDA levels, compared to the control group. Since vitamin E is a powerful antioxidant with anti-inflammatory properties and the main mechanism of OS in HD is the exposure of blood to the artificial dialyzer, coating the inner surface of HD membranes with vitamin E was an attractive approach to ameliorate OS. Data

from meta-analyses have coherently showed that HD with vitamin E coated membranes significantly decreased MDA and TBARS (68), improved anemia and decreased both inflammation (69) and OS status (70).

In PD, the most promising antioxidant that has been studied is NAC, a ROS scavenger that might decrease accumulation of AGEs and inflammatory cytokines in the peritoneal cavity (6, 18, 71). Two studies in PD cohorts independently reported that oral NAC supplementation decreased OS, suppressed inflammation, preserved residual renal function and protected the peritoneal membrane from OS-derived sclerosis and injury (72, 73).

Conclusion

OS is highly prevalent even at early stages of CKD and gradually increases with deterioration of kidney function. In ESKD, OS is further aggravated and is associated with adverse events, including CV disease and mortality. In HD patients, the main pathogenetic mechanism underlying the generation of free radicals is the contact of blood with the artificial, synthetic, bioincompatible dialyzer membranes and dialysate. PD patients suffer from lesser degree of OS compared to HD patients, mainly due to the composition of PD fluids. To date, there are no specific guidelines regarding the supplementation of antioxidant agents to ameliorate the increased OS in HD or PD patients. Future, large, randomized, placebo-controlled trials are required to draw definite conclusions.

References

1. McCullough KP, Morgenstern H, Saran R, Herman WH, Robinson BM. Projecting ESRD incidence and prevalence in the United States through 2030. Journal of the American Society of Nephrology. 2019;30(1): 127-35. [CrossRef] [PubMed]
2. Roumeliotis A, Roumeliotis S, Panagoutsos S, Theodoridis M, Argyriou C, Tavridou A, et al. Carotid intima-media thickness is an independent predictor of all-cause mortality and cardiovascular morbidity in patients with diabetes mellitus type 2 and chronic kidney disease. Ren Fail. 2019;41(1):131-8. [CrossRef] [PubMed]
3. Fox CS, Matsushita K, Woodward M, Bilo HJ, Chalmers J, Heerspink HJ, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet. 2012;380(9854):1662-73. [CrossRef] [PubMed]
4. Collins AJ, Foley RN, Gilbertson DT, Chen S-C. United States Renal Data System public health surveillance of chronic kidney disease and end-stage renal disease. Kidney international supplements. 2015;5(1):2-7. [CrossRef] [PubMed]
5. Roumeliotis S, Roumeliotis A, Dounousi E, Eleftheriadis T, Liakopoulos V. Dietary Antioxidant Supplements and Uric Acid in Chronic Kidney Disease: A Review. Nutrients. 2019;11(8). [CrossRef] [PubMed]
6. Roumeliotis S, Roumeliotis A, Gorny X, Mertens P. Could antioxidant supplementation delay progression of cardiovascular disease in end-stage renal disease patients? Curr Vasc Pharmacol. 2021;19(1):41-54. [CrossRef] [PubMed]
7. Roumeliotis S, Veljkovic A, Georgianos PI, Lazarevic G, Perisic Z, Hadzi-Djokic J, et al. Association between Biomarkers of Oxidative Stress and Inflammation with Cardiac Necrosis and Heart Failure in Non-ST Segment Elevation Myocardial Infarction Patients and Various Degrees of Kidney Function. Oxid Med Cell Longev. 2021;2021:3090120. [CrossRef] [PubMed]
8. Locatelli F, Canaud B, Eckardt KU, Stenvinkel P, Wanner C, Zoccali C. Oxidative stress in end-stage renal disease: an emerging threat to patient outcome. Nephrol Dial Transplant. 2003;18(7):1272-80. [CrossRef] [PubMed]
9. Liakopoulos V, Roumeliotis S, Zarogiannis S, Eleftheriadis T, Mertens PR. Oxidative stress in hemodialysis: Causative mechanisms, clinical implications, and possible therapeutic interventions. Semin Dial. 2019;32(1):58-71. [CrossRef] [PubMed]
10. Yilmaz MI, Saglam M, Caglar K, Cakir E, Sonmez A, Ozgurtas T, et al. The determinants of endothelial dysfunction in CKD: oxidative stress and asymmetric dimethylarginine. Am J Kidney Dis. 2006;47(1):42-50. [CrossRef] [PubMed]
11. Dounousi E, Papavasiliou E, Makedou A, Ioannou K, Katopodis KP, Tselepis A, et al. Oxidative stress is progressively enhanced with advancing stages of CKD. American Journal of Kidney Diseases. 2006;48(5): 752-60. [CrossRef] [PubMed]
12. Himmelfarb J. Linking oxidative stress and inflammation in kidney disease: which is the chicken and which is the egg? Semin Dial. 2004;17(6):449-54. [CrossRef] [PubMed]
13. Himmelfarb J. Uremic toxicity, oxidative stress, and hemodialysis as renal replacement therapy. Semin Dial. 2009;22(6):636-43. [CrossRef] [PubMed]

14. Simmons EM, Langone A, Sezer MT, Vella JP, Recupero P, Morrow JD, et al. Effect of renal transplantation on biomarkers of inflammation and oxidative stress in end-stage renal disease patients. Transplantation. 2005;79(8):914-9. [CrossRef] [PubMed]
15. Canaud B, Cristol J, Morena M, Leray-Moragues H, Bosc J, Vaussenat F. Imbalance of oxidants and antioxidants in haemodialysis patients. Blood Purif. 1999; 17(2-3):99-106. [CrossRef] [PubMed]
16. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med. 1999;340(2):115-26. [CrossRef] [PubMed]
17. Liakopoulos V, Roumeliotis S, Gorny X, Dounousi E, Mertens PR. Oxidative Stress in Hemodialysis Patients: A Review of the Literature. Oxid Med Cell Longev. 2017;2017:3081856. [CrossRef] [PubMed]
18. Liakopoulos V, Roumeliotis S, Bozikas A, Eleftheriadis T, Dounousi E. Antioxidant Supplementation in Renal Replacement Therapy Patients: Is There Evidence? Oxid Med Cell Longev. 2019;2019:9109473. [CrossRef] [PubMed]
19. Chen MF, Chang CL, Liou SY. Increase in resting levels of superoxide anion in the whole blood of uremic patients on chronic hemodialysis. Blood Purif. 1998; 16(5):290-300. [CrossRef] [PubMed]
20. Nguyen AT, Lethias C, Zingraff J, Herbelin A, Naret C, Descamps-Latscha B. Hemodialysis membrane-induced activation of phagocyte oxidative metabolism detected in vivo and in vitro within microamounts of whole blood. Kidney Int. 1985;28(2):158-67. [CrossRef] [PubMed]
21. Yang CC, Hsu SP, Wu MS, Hsu SM, Chien CT. Effects of vitamin C infusion and vitamin E-coated membrane on hemodialysis-induced oxidative stress. Kidney Int. 2006;69(4):706-14. [CrossRef] [PubMed]
22. Bayes B, Pastor MC, Bonal J, Foraster A, Romero R. Oxidative stress, inflammation and cardiovascular mortality in haemodialysis--role of seniority and intravenous ferrotherapy: analysis at 4 years of follow-up. Nephrol Dial Transplant. 2006;21(4):984-90. [CrossRef] [PubMed]
23. Morena M, Cristol JP, Bosc JY, Tetta C, Forret G, Leger CL, et al. Convective and diffusive losses of vitamin C during haemodiafiltration session: a contributive factor to oxidative stress in haemodialysis patients. Nephrol Dial Transplant. 2002;17(3):422-7. [CrossRef] [PubMed]
24. Dasgupta A, Hussain S, Ahmad S. Increased lipid peroxidation in patients on maintenance hemodialysis. Nephron. 1992;60(1):56-9. [CrossRef] [PubMed]
25. Varan HI, Dursun B, Dursun E, Ozben T, Suleymanlar G. Acute effects of hemodialysis on oxidative stress parameters in chronic uremic patients: comparison of two dialysis membranes. Int J Nephrol Renovasc Dis. 2010;3:39-45. [CrossRef] [PubMed]
26. Cristol JP, Canaud B, Rabesandratana H, Gaillard I, Serre A, Mion C. Enhancement of reactive oxygen species production and cell surface markers expression due to haemodialysis. Nephrol Dial Transplant. 1994;9(4):389-94. [PubMed]
27. Descamps-Latscha B, Goldfarb B, Nguyen AT, Landais P, London G, Haeffner-Cavaillon N, et al. Establishing the relationship between complement activation and stimulation of phagocyte oxidative metabolism in hemodialyzed patients: a randomized prospective study. Nephron. 1991;59(2):279-85. [CrossRef] [PubMed]
28. Kosch M, Levers A, Fobker M, Barenbrock M, Schaefer RM, Rahn KH, et al. Dialysis filter type determines the acute effect of haemodialysis on endothelial function and oxidative stress. Nephrol Dial Transplant. 2003; 18(7):1370-5. [CrossRef] [PubMed]
29. Biasioli S, Schiavon R, Petrosino L, Cavallini L, Zambello A, De Fanti E, et al. Free radicals and oxidative stress challenge dialysis patients: effects of two different membranes. ASAIO J. 1997;43(5): M766-72. [PubMed]
30. Maher ER, Wickens DG, Griffin JF, Kyle P, Curtis JR, Dormandy TL. Increased free-radical activity during haemodialysis? Nephrol Dial Transplant. 1987;2(3): 169-71. PubMed]
31. Bos JC, Grooteman MP, van Houte AJ, Schoorl M, van Limbeek J, Nube MJ. Low polymorphonuclear cell degranulation during citrate anticoagulation: a comparison between citrate and heparin dialysis. Nephrol Dial Transplant. 1997;12(7):1387-93. [CrossRef] [PubMed]
32. Gritters M, Grooteman MP, Schoorl M, Schoorl M, Bartels PC, Scheffer PG, et al. Citrate anticoagulation abolishes degranulation of polymorphonuclear cells and platelets and reduces oxidative stress during haemodialysis. Nephrol Dial Transplant. 2006;21(1): 153-9. [CrossRef] [PubMed]
33. Lonnemann G. Chronic inflammation in hemodialysis: the role of contaminated dialysate. Blood Purif. 2000; 18(3):214-23. [CrossRef] [PubMed]
34. Masakane I. Review: Clinical usefulness of ultrapure dialysate--recent evidence and perspectives. Ther Apher Dial. 2006;10(4):348-54. [CrossRef] [PubMed]
35. Arizono K, Nomura K, Motoyama T, Matsushita Y, Matsuoka K, Miyazu R, et al. Use of ultrapure dialysate in reduction of chronic inflammation during hemodialysis. Blood Purif. 2004;22 Suppl 2:26-9. [CrossRef] [PubMed]
36. Furuya R, Kumagai H, Takahashi M, Sano K, Hishida A. Ultrapure dialysate reduces plasma levels of beta2-microglobulin and pentosidine in hemodialysis patients. Blood Purif. 2005;23(4):311-6. [CrossRef] [PubMed]
37. Schiffl H, Lang SM, Stratakis D, Fischer R. Effects of ultrapure dialysis fluid on nutritional status and inflammatory parameters. Nephrol Dial Transplant. 2001;16(9):1863-9. [CrossRef] [PubMed]
38. Susantitaphong P, Riella C, Jaber BL. Effect of ultrapure dialysate on markers of inflammation, oxidative stress, nutrition and anemia parameters: a meta-analysis. Nephrol Dial Transplant. 2013;28(2):438-46. [CrossRef] [PubMed]
39. Weiss MF, Scivittaro V, Anderson JM. Oxidative stress and increased expression of growth factors in lesions of failed hemodialysis access. Am J Kidney Dis. 2001; 37(5):970-80. [CrossRef] [PubMed]
40. 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):1524-38. [CrossRef] [PubMed]
41. Wiswedel I, Peter D, Gardemann A, Carluccio F, Hampl H, Siems W. Serum Concentrations of F2-Isoprostanes and 4-Hydroxynonenal in Hemodialysis Patients in Relation to Inflammation and Renal Anemia. Biomark Insights. 2008;3:419-28. [CrossRef] [PubMed]
42. Sommerburg O, Grune T, Hampl H, Riedel E, Ehrich JH, Siems WG. Does treatment of renal anemia with recombinant erythropoietin influence oxidative stress in hemodialysis patients? Clin Nephrol. 2000; 53(1 Suppl):S23-9. [PubMed]
43. Siems W, Carluccio F, Radenkovic S, Grune T, Hampl H. Oxidative stress in renal anemia of hemodialysis patients is mitigated by epoetin treatment. Kidney Blood Press Res. 2005;28(5-6):295-301. [CrossRef] [PubMed]
44. Sommerburg O, Grune T, Hampl H, Riedel E, van Kuijk FJ, Ehrich JH, et al. Does long-term treatment of

renal anaemia with recombinant erythropoietin influence oxidative stress in haemodialysed patients? Nephrol Dial Transplant. 1998;13(10):2583-7. [CrossRef] [PubMed]
45. Katavetin P, Tungsanga K, Eiam-Ong S, Nangaku M. Antioxidative effects of erythropoietin. Kidney Int Suppl. 2007(107):S10-5. [CrossRef] [PubMed]
46. Agarwal R, Vasavada N, Sachs NG, Chase S. Oxidative stress and renal injury with intravenous iron in patients with chronic kidney disease. Kidney Int. 2004; 65(6):2279-89.
47. Agarwal R, Warnock D. Issues related to iron replacement in chronic kidney disease. Semin Nephrol. 2002;22(6):479-87. [CrossRef] [PubMed]
48. Hasselwander O, Young IS. Oxidative stress in chronic renal failure. Free Radic Res. 1998;29(1):1-11. [CrossRef]
49. Roob JM, Khoschsorur G, Tiran A, Horina JH, Holzer H, Winklhofer-Roob BM. Vitamin E attenuates oxidative stress induced by intravenous iron in patients on hemodialysis. J Am Soc Nephrol. 2000;11(3):539-49. [CrossRef] [PubMed]
50. Muller C, Eisenbrand G, Gradinger M, Rath T, Albert FW, Vienken J, et al. Effects of hemodialysis, dialyser type and iron infusion on oxidative stress in uremic patients. Free Radic Res. 2004;38(10):1093-100. [CrossRef] [PubMed]
51. Tovbin D, Mazor D, Vorobiov M, Chaimovitz C, Meyerstein N. Induction of protein oxidation by intravenous iron in hemodialysis patients: role of inflammation. Am J Kidney Dis. 2002;40(5):1005-12. [CrossRef] [PubMed]
52. Kato A, Odamaki M, Takita T, Furuhashi M, Maruyama Y, Hishida A. C-reactive protein is a predictor of short-term mortality in hemodialysis patients. Am J Nephrol. 2001;21(2):176-8. [CrossRef] [PubMed]
53. Goldstein SL, Currier H, Watters L, Hempe JM, Sheth RD, Silverstein D. Acute and chronic inflammation in pediatric patients receiving hemodialysis. J Pediatr. 2003;143(5):653-7. [CrossRef] [PubMed]
54. Malindretos P, Sarafidis PA, Rudenco I, Raptis V, Makedou K, Makedou A, et al. Slow intravenous iron administration does not aggravate oxidative stress and inflammatory biomarkers during hemodialysis: a comparative study between iron sucrose and iron dextran. Am J Nephrol. 2007;27(6):572-9. [CrossRef] [PubMed]
55. Weiss G, Meusburger E, Radacher G, Garimorth K, Neyer U, Mayer G. Effect of iron treatment on circulating cytokine levels in ESRD patients receiving recombinant human erythropoietin. Kidney Int. 2003; 64(2):572-8. [CrossRef] [PubMed]
56. Jain AK, Blake P, Cordy P, Garg AX. Global trends in rates of peritoneal dialysis. Journal of the American Society of Nephrology. 2012;23(3):533-44. [CrossRef] [PubMed]
57. Liakopoulos V, Roumeliotis S, Gorny X, Eleftheriadis T, Mertens PR. Oxidative Stress in Patients Undergoing Peritoneal Dialysis: A Current Review of the Literature. Oxid Med Cell Longev. 2017;2017:3494867. [CrossRef] [PubMed]
58. Brunkhorst R, Mahiout A. Pyruvate neutralizes peritoneal dialysate cytotoxicity: Maintained integrity and proliferation of cultured human mesothelial cells. Kidney international. 1995;48(1):177-81. [CrossRef] [PubMed]
59. Roumeliotis S, Eleftheriadis T, Liakopoulos V. Is oxidative stress an issue in peritoneal dialysis? Semin Dial. 2019;32(5):463-6. [CrossRef] [PubMed]
60. Roumeliotis S, Dounousi E, Salmas M, Eleftheriadis T, Liakopoulos V. Unfavorable Effects of Peritoneal Dialysis Solutions on the Peritoneal Membrane: The Role of Oxidative Stress. Biomolecules. 2020;10(5). [CrossRef]
61. Raimann JG, Levin NW, Craig RG, Sirover W, Kotanko P, Handelman G. Is vitamin C intake too low in dialysis patients? Semin Dial. 2013;26(1):1-5. [CrossRef] [PubMed]
62. Chan D, Irish A, Croft KD, Dogra G. Effect of ascorbic acid supplementation on plasma isoprostanes in haemodialysis patients. Nephrol Dial Transplant. 2006;21(1):234-5. [CrossRef] [PubMed]
63. Washio K, Inagaki M, Tsuji M, Morio Y, Akiyama S, Gotoh H, et al. Oral vitamin C supplementation in hemodialysis patients and its effect on the plasma level of oxidized ascorbic acid and Cu/Zn superoxide dismutase, an oxidative stress marker. Nephron Clin Pract. 2008;109(2):c49-54. [CrossRef] [PubMed]
64. Chan D, Irish A, Dogra G. Efficacy and safety of oral versus intravenous ascorbic acid for anaemia in haemodialysis patients. Nephrology (Carlton). 2005; 10(4):336-40. [CrossRef] [PubMed]
65. Fumeron C, Nguyen-Khoa T, Saltiel C, Kebede M, Buisson C, Drueke TB, et al. Effects of oral vitamin C supplementation on oxidative stress and inflammation status in haemodialysis patients. Nephrol Dial Transplant. 2005;20(9):1874-9. [CrossRef] [PubMed]
66. De Vriese AS, Borrey D, Mahieu E, Claeys I, Stevens L, Vanhaeverbeke A, et al. Oral vitamin C administration increases lipid peroxidation in hemodialysis patients. Nephron Clin Pract. 2008;108(1):c28-34. [CrossRef] [PubMed]
67. Nguyen TTU, Yeom JH, Kim W. Beneficial Effects of Vitamin E Supplementation on Endothelial Dysfunction, Inflammation, and Oxidative Stress Biomarkers in Patients Receiving Hemodialysis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Int J Mol Sci. 2021;22(21). [CrossRef] [PubMed]
68. Sosa MA, Balk EM, Lau J, Liangos O, Balakrishnan VS, Madias NE, et al. A systematic review of the effect of the Excebrane dialyser on biomarkers of lipid peroxidation. Nephrol Dial Transplant. 2006;21(10): 2825-33. [CrossRef] [PubMed]
69. D'Arrigo G, Baggetta R, Tripepi G, Galli F, Bolignano D. Effects of Vitamin E-Coated versus Conventional Membranes in Chronic Hemodialysis Patients: A Systematic Review and Meta-Analysis. Blood Purif. 2017; 43(1-3):101-22. [CrossRef] [PubMed]
70. Yang SK, Xiao L, Xu B, Xu XX, Liu FY, Sun L. Effects of vitamin E-coated dialyzer on oxidative stress and inflammation status in hemodialysis patients: a systematic review and meta-analysis. Ren Fail. 2014; 36(5):722-31. [CrossRef] [PubMed]
71. Roumeliotis S, Eleftheriadis T, Liakopoulos V. Is oxidative stress an issue in peritoneal dialysis? Semin Dial. 2019;32(5):463-6. [CrossRef] [PubMed]
72. Feldman L, Shani M, Efrati S, Beberashvili I, Yakov-Hai I, Abramov E, et al. N-acetylcysteine improves residual renal function in peritoneal dialysis patients: a pilot study. Perit Dial Int. 2011;31(5):545-50. [CrossRef] [PubMed]
73. Nascimento MM, Suliman ME, Silva M, Chinaglia T, Marchioro J, Hayashi SY, et al. Effect of oral N-acetylcysteine treatment on plasma inflammatory and oxidative stress markers in peritoneal dialysis patients: a placebo-controlled study. Perit Dial Int. 2010; 30(3):336-42. [CrossRef] [PubMed]

Pregledni rad **UDC: 616.61:577.1**
doi:10.5633/amm.2022.0207

IMPLIKACIJE OKSIDATIVNOG STRESA KOD BOLESNIKA U ZAVRŠNOJ FAZI HRONIČNE BOLESTI BUBREGA: PREGLED KAUZATIVNIH MEHANIZAMA I TRENUTNIH KONCEPATA

Vassilios Liakopoulos[1,2], Garyfallia Varouktsi[1,2], Ariti Tsinari[1,2], Andrej Veljković[3], Gordana Lazarević[4,5], Zoran Perišić[4,5], Jovan Hadži-Đokić[6], Gordana Kocić[3], Stefanos Roumeliotis[1,2]

[1]Odeljenje za nefrologiju i hipertenziju, Prvi departman interne medicine, AHEPA bolnica, Solun, Grčka
[2]Aristotelov univerzitet u Solunu, Medicinski fakultet, Solun, Grčka
[3]Univerzitet u Nišu, Medicinski fakultet, Katedra za biohemiju, Niš, Srbija
[4]Univerzitetski klinički centar Niš, Klinika za kardiologiju, Niš, Srbija
[5]Univerzitet u Nišu, Medicinski fakultet, Katedra Interna medicina i zdravstvena nega, Niš, Srbija
[6]Srpska akademija nauka i umetnosti, Beograd, Srbija

Kontakt: Vassilios Liakopoulos
Kyriakidi 1, 54636 Solun, Grčka
E-mail: vliak@auth.gr

Oksidativni stres (OS), označen kao disbalans između antioksidanasa i prooksidanasa, u korist potonjih, ima izraženu prevalenciju kod hronične bolesti bubrega (HBB), čak i u ranim fazama bolesti i postepeno se povećava, paralelno sa deterioracijom bubrega. U završnoj fazi hronične bolesti bubrega, OS se dalje pogoršava i povezuje se različitim nepovoljnim ishodima, uključujući aterosklerozu i kardiovaskularne bolesti. U ovom pregledu, cilj je da predstavimo kliničke implikacije OS, patogenetske kauzativne mehanizme i potencijalne terapeutske intervencije, kod bolesnika na hemodijalizi i peritonealnoj dijalizi.

Acta Medica Medianae 2022;61(2):53-59.

Ključne reči: *kardiovaskularne bolesti, hronična bolest bubrega, završna faza hronične bolesti bubrega, hemodijaliza, oksidativni stres, peritonealna dijaliza, vitamin C, vitamin E*