

MICROINFLAMMATION IN PATIENTS ON HEMODIALYSIS: A PRACTICAL APPROACH

Marko Nenadovic¹, Aleksandra Nikolic², Marijana Stanojevic Pirkovic³, Tomislav Nikolic^{1,4},
Dejan Petrovic^{1,4} and Jasna Trbojevic-Stankovic^{5,6}

¹Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia

²Clinic of Internal Medicine, Clinical Center Kragujevac, Kragujevac, Serbia

³Department of Biochemistry, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia

⁴Clinic of Urology, Nephrology and Dialysis, University Clinical Center Kragujevac, Kragujevac, Serbia

⁵Faculty of Medicine, University of Belgrade, Belgrade, Serbia

⁶University Hospital Center "Dr Dragisa Misovic - Dedinje", Belgrade, Serbia

Received: 01.10.2021

Accepted: 15.10.2021.

ABSTRACT

Microinflammation is a non-traditional risk factor for the development of cardiovascular diseases in patients on hemodialysis. It occurs in 30-50% of these patients, and its main causes are: uremic toxins, oxidative stress, metabolic acidosis, vitamin D deficiency, overhydration, altered intestinal microbiome, impaired intestinal epithelial barrier integrity, increased translocation of endotoxin from the intestinal lumen into the systemic circulation, occult infection of the vascular approach for hemodialysis, periodontal disease, bioincompatibility of the hemodialysis membrane and the presence of endotoxin in the hemodialysis solution. The main clinical consequences of microinflammation are: accelerated atherosclerosis, malnutrition, anemia, resistance to the action of erythropoietin, hemoglobin variability and dialysis-related amyloidosis. Postdilution online hemodiafiltration, extended and adsorptive hemodialysis prevent the development of microinflammation. Optimal control of microinflammation prevents the development of cardiovascular diseases, improves the quality of life and the outcome of patients who are treated with regular hemodialysis.

Keywords: Microinflammation, postdilution online hemodiafiltration, extended hemodialysis, adsorptive hemodialysis.

Corresponding author:

Prof. dr Dejan Petrovic

Faculty of Medical Sciences, University of Kragujevac,
Clinic of Urology, Nephrology and Dialysis, University
Clinical Center Kragujevac, Kragujevac, Serbia

E-mail: dejan.petrovic@fmn.kg.ac.rs



UDK: 616.12:616.61-78-056.24

Ser J Exp Clin Res 2024; 25(2):171-179

DOI: 10.2478/sjecr-2021-0047

INTRODUCTION

Cardiovascular diseases are the leading cause of death in patients treated with regular hemodialysis (1-4). Uremic toxins, microinflammation, malnutrition, oxidative stress, endothelial dysfunction, erythropoietin resistance and anemia are significant non-traditional risk factors for the development of cardiovascular disease. Microinflammation occurs in 30-50% of patients on hemodialysis, and its main clinical consequences are: accelerated atherosclerosis, malnutrition and resistance to the action of erythropoietin. Microinflammation plays a key role in the process of atherosclerosis, development and rupture of atherosclerotic plaque, and its early detection and timely application of appropriate treatment significantly reduce the development of cardiovascular morbidity and mortality in patients treated with hemodialysis (5). Early detection and optimal control of nontraditional risk factors play a key role in preventing the development of cardiovascular disease in this patient population (4-6).

Definition and etiopathogenesis of microinflammation

Microinflammation is defined as a pathological condition, which is characterized by constant low-grade inflammation followed by an increase in the concentration of pro-inflammatory mediators in the serum (concentration of C-reactive protein - CRP ≥ 10 mg/L, IL-6 concentration ≥ 7 pg/mL) (7). The etiopathogenesis of microinflammation is complex and includes multiple factors: uremic toxins, immune system dysfunction in chronic kidney disease, intestinal microbiome dysfunction, dialysis membrane biocompatibility, conventional dialysis solution, presence of endotoxin in dialysis solution, reversible ultrasound hemodialysis, gingival infection (periodontitis), increased extracellular fluid volume (overhydration), metabolic acidosis, vitamin D deficiency (7, 8).

Uremic toxins play a significant role in the development of microinflammation, oxidative stress, accelerated atherosclerosis, and cardiovascular disease in this patient population (8-10). According to the recommendations of the EUTox (European Union Toxin Working Group), uremic toxins are divided into three groups. The first group consists of uremic toxins of low molecular weight (MW < 500 Da). These toxins are soluble in water and are effectively removed by standard high-flux hemodialysis. The second group consists of uremic toxins that bind in a high percentage to plasma proteins (degree of binding to plasma proteins > 90%). They are mainly low molecular weight (MW < 500 Da) and are efficiently removed by hemodialysis with membranes that have the ability to adsorb. Middle molecular weight uremic toxins (MW = 0.5-60 kDa) belong to the third group of uremic toxins. These uremic toxins are effectively removed by postdilution online hemodiafiltration and extended hemodialysis - ED (Expanded Dialysis). Middle molecular weight uremic toxins include proinflammatory cytokines (interleukin-1 β , interleukin-6, interleukin-18, tumor necrosis factor alpha - TNF α), proinflammatory proteins (pentraxin-3, YKL-40) and adipokines (adiponectin, visfatin, leptin). Proinflammatory cytokines, proteins and adipokines play a significant role in the

development of microinflammation and malnutrition in patients treated with regular hemodialysis. Microinflammation, malnutrition and oxidative stress are significant non-traditional risk factors, which result in the development of accelerated atherosclerosis (atherosclerotic cardiovascular disease), amyloidosis associated with hemodialysis, erythropoietin resistance, and anemia (8-10).

In the end-stage of chronic kidney disease, due to the accumulation of uremic toxins, the function of the immune system is disturbed. We distinguish between disorders of the innate and acquired immune system. Disorders of the innate immune system in patients on hemodialysis include: constant activation of neutrophils and low-grade peripheral blood monocytes, which results in an increased risk of developing microinflammation and atherosclerotic cardiovascular diseases. Due to the reduced function of phagocytosis of neutrophils and monocytes, as well as the reduced function of NK cells, the risk of bacterial infections is increased. Disorder of the acquired immune system is characterized by a decrease in the number and function of B and T lymphocytes, which results in an increased risk of viral infections and malignant diseases (11). The two most significant uremic toxins that alter the function of the immune system in this patient population are indoxyl sulfate and p-cresyl sulfate. Indoxyl sulfate stimulates monocytes to enhance the production and release of proinflammatory cytokines, while p-cresyl sulfate reduces phagocytosis function and NADPH oxidase activity in neutrophils, as well as antigen presentation by dendritic cells (11).

Hemodialysis membranes play a key role in the process of hemodialysis and hemodiafiltration. They can be natural or artificial (synthetic). Natural membranes are derivatives of cellulose (cuprophane), they are "low-flux", they are less biocompatible compared to synthetic membranes and they have a small clearance of uremic toxins of middle molecular weight. Synthetic membranes (polysulfone, polyethersulfone, polyarylethersulfone, ethylene vinyl alcohol, polyamide, polyacrylonitrile, polymethylacrylate, helixone) are highly biocompatible "high-flux" membranes, which have a good clearance of middle molecular weight uremic toxins (12-14). The composition of the dialysis membrane (cellulose membrane), the sterilization method (ethylene oxide) and bisphenol A can be triggers of bioincompatibility reactions. During hemodialysis, the blood comes into direct contact with the synthetic material of the dialysis membrane and extracorporeal circulation, and as a consequence various reactions can occur: activation of neutrophils and peripheral blood monocytes, activation of the complement system, activation of coagulation and platelet systems, hypersensitivity reactions (allergic reactions). Activated neutrophils increase the production and release of proteinases (elastase, myeloperoxidase), lactoferrin, cathepsin, chemokines (IL-8, CCL2, CCL3) and cytokines (IL-1, IL-6, TNF α , TGF β). Released mediators intensify microinflammation. In clinical practice, the concentration of neutrophilic elastase and myeloperoxidase (released from granules due to neutrophil activation) in serum is measured to assess the biocompatibility of the

dialysis membrane, while the concentration of platelet factor 4 and β -thromboglobulin is measured to assess platelet activation. All of these serum parameters are measured at the start of the dialysis session, after 15 minutes, 60 minutes, and at the end of the dialysis session (12-14). Due to the activation of neutrophils and peripheral blood monocytes, there is an increased production of oxygen free radicals, and due to increased loss of trace elements and water-soluble antioxidants during the hemodialysis session, the activity of antioxidant enzymes decreases (increased oxidative stress) (12-14).

Allergic reactions associated with hemodialysis are classified as type A and type B reactions. Type A reactions occur 5-30 minutes after the start of dialysis, are mediated by IgE class antibodies (anaphylactic reactions), releasing histamine, leukotrienes, prostaglandins and cytokines from mast cells and basophils, resulting in itching, runny nose, abdominal cramps, tingling in the vascular approach to hemodialysis, urticaria, bronchospasm, angioedema, and anaphylactic shock (15, 16). Type A reactions are repeated when the same type of dialyzer is used. Type B reactions occur later (> 30 minutes from the start of the hemodialysis session), are not mediated by IgE class antibodies (anaphylactoid reactions), are triggered by activation of the complement system, clinical symptoms are less pronounced: headache, nausea, vomiting, back and/or chest pain, hypotension (15, 16).

The microbiological quality of the hemodialysis solution is a risk factor for the development of microinflammation and accelerated atherosclerosis. During the hemodialysis session, bacterial products (endotoxins) through the processes of backdiffusion and back ultrafiltration (backdiffusion/backfiltration) from the dialysis solution, through the dialysis membrane, reach the patient's blood and activate monocytes. Activated monocytes intensively produce and release pro-inflammatory cytokines (IL-1, IL-6, TNF α), which results in the development of persistent low-grade microinflammation and the development of accelerated atherosclerosis. High-flux hemodialysis, postdilution online hemodiafiltration, and extended hemodialysis require an ultrapure dialysis solution. It is defined as a solution in which the bacterial concentration is < 0.1 CFU/mL and the endotoxin concentration is less than 0.03 EU/mL. In postdilution online hemodiafiltration, a sterile substitution solution is used, and it is defined as a solution in which the bacterial concentration is < 10⁻⁶ CFU/mL and the endotoxin concentration is less than 0.03 EU/mL (17).

Metabolic acidosis occurs in 15-20% of patients with chronic kidney disease. It is defined as a serum bicarbonate concentration of less than 22 mmol/L. The main clinical consequences of metabolic acidosis are: microinflammation, increased protein catabolism (decrease in muscle mass), progression of chronic kidney disease, development of osteoporosis, insulin resistance, decreased albumin synthesis in the liver (hypoalbuminemia), increased risk of adverse outcome in these patients. The target serum bicarbonate concentration in patients with chronic kidney disease should be - HCO₃⁻ $\geq$ 22 mmol/L (optimal HCO₃⁻ concentration should be: 22-26 mmol/L) (21, 22). For the treatment of metabolic acidosis,

sodium bicarbonate (650 mg tablets) is used twice a day until the target serum bicarbonate concentration is reached (18, 19).

Oxidative stress is a non-traditional risk factor for the development of cardiovascular diseases in the population of patients treated with regular hemodialysis. Hemodialysis is itself a trigger for increased oxygen free radical formation. The two main pathophysiological mechanisms of enhanced oxygen free radical formation during a hemodialysis session are: bioincompatibility of the dialysis membrane and the presence of endotoxin in the dialysis solution. In contact with the blood and the dialysis membrane, NADPH neutrophil oxidase is activated, oxygen free radicals are formed, and myeloperoxidase - MPO (Myeloperoxidase) is released from the neutrophil granules. Measurement of serum myeloperoxidase concentration during a hemodialysis session is an indicator of the severity of oxidative stress induced by a bioincompatible dialysis membrane. Endotoxin and other bacterial products, through backdiffusion/backfiltration processes, pass from the dialysis solution through the dialysis membrane into the patient's circulation and activate neutrophils and monocytes to increase the production and release of oxygen free radicals and proinflammatory cytokines. This results in the development of oxidative stress, microinflammation and accelerated atherosclerosis. In patients treated with regular hemodialysis, the activity of enzymatic and non-enzymatic antioxidant systems is reduced. During the hemodialysis session, trace elements (zinc, selenium, copper) are lost, and this results in reduced activity of antioxidant enzymes, such as superoxide dismutase and glutathione peroxidase. Vitamin E-coated dialysis membrane reduces the concentration of lipid peroxidation parameters in the serum of patients treated with high-flux hemodialysis and postdilution online hemodiafiltration (20, 21).

Intestinal microbiome disorder (intestinal dysbiosis) is defined as a change in the composition and function of intestinal microorganisms. Studies show that intestinal microbiome disorder is a non-traditional risk factor for the development of cardiovascular disease in patients treated with regular hemodialysis. As a consequence of intestinal microbiome disorders, indoxyl sulfate and p-cresyl sulfate are increasingly formed. These uremic toxins bind in a high percentage to plasma proteins, are poorly removed by high-flux hemodialysis, extended hemodialysis, and postdilution online hemodiafiltration. They stimulate the activation and adhesion of leukocytes to endothelial cells, increase and release inflammatory mediators, stimulate oxidative stress and the formation of foam cells, cause endothelial dysfunction and reduced production of nitric oxide, which begins the process of atherosclerosis (atherosclerotic plaque). High-flux hemodialysis with adsorptive membranes and the oral adsorbent AST-120 play a significant role in reducing the concentration of indoxyl sulfate and preventing the development of atherosclerotic cardiovascular diseases in patients treated with regular hemodialysis (22). Intestinal microbiome disorders and intestinal epithelial barrier integrity disorders play a significant role in the development of microinflammation in

patients treated with regular hemodialysis. Due to the disturbed epithelial barrier of the intestine, bacteria and endotoxins are translocated from the intestinal lumen into the systemic circulation, which activate the innate immune system. Through so many receptors, neutrophils and peripheral blood monocytes are activated, they increase the production and release of proinflammatory mediators (cytokines), resulting in systemic microinflammation (22).

High-flux hemodialysis with adsorptive membranes and the oral adsorbent AST-120 play a significant role in reducing the concentration of indoxyl sulfate and preventing the development of atherosclerotic cardiovascular diseases in patients treated with regular hemodialysis (22). Intestinal microbiome disorders and intestinal epithelial barrier integrity disorders play a significant role in the development of microinflammation in patients treated with regular hemodialysis. Due to the disturbed epithelial barrier of the intestine, bacteria and endotoxins are translocated from the intestinal lumen into the systemic circulation, which activate the innate immune system. Through so many receptors, neutrophils and peripheral blood monocytes are activated, they increase the production and release of proinflammatory mediators (cytokines), resulting in systemic microinflammation (22).

Overhydration is defined as an increase in the volume of extracellular fluid in patients treated with regular hemodialysis. It is a risk factor for the development of microinflammation, malnutrition and cardiovascular diseases. Overhydration causes edema of the intestinal wall and increased translocation of bacteria and endotoxins from the intestinal lumen into the systemic circulation. As a consequence of the activation of the cells of the innate immune system, there is an increased production and secretion of proinflammatory cytokines and the development of microinflammation. The following parameters are used to assess the state of hydration: overhydration (OH) and the ratio of overhydration to extracellular fluid volume (OH/ECW). Normal hydration in hemodialysis patients is present if the OH is in the range of -1.1 to +1.1 liters. Mild hyperhydration exists if OH = 1.1-2.5 liters, and severe excess fluid is defined as OH > 2.5 liters. The OH/ECW ratio > 15% in men and > 13% in women indicates overhydration. Patients treated with hemodialysis in whom OH > 2.5 liters and OH/ECW ratio > 15% have a statistically significantly higher mortality rate compared to patients with normal hydration (23-26).

Vitamin D [25 (OH) D] reduces microinflammation, resistance to the action of erythropoietin, has a protective effect on the cardiovascular and immune system of patients treated with regular hemodialysis. In patients treated with regular hemodialysis, the normal concentration of vitamin D [25 (OH) D] is 30-80 ng/mL, and vitamin D deficiency is defined as a vitamin D concentration of less than 30 ng/mL. Patients with a serum vitamin D concentration of 20-30 ng/mL have a mild deficiency, and a serum vitamin D concentration of 10-20 ng/mL indicates a moderate deficiency. Severe vitamin D deficiency is defined as a vitamin D concentration of less than 10 ng/mL. Vitamin D substitution involves the

administration of ergocalciferol or cholecalciferol at a dose of 25,000 IU/week for 3-6 months. In case of severe vitamin D deficiency (< 10 ng/mL), ergocalciferol or cholecalciferol should be administered at a dose of 50,000 IU/week for three to six weeks, until the target serum vitamin D concentration ≥ 30 ng/mL (27).

Clinical consequences of microinflammation

Atherosclerosis and atherosclerotic cardiovascular disease

Microinflammation, oxidative stress, and hyperhomocysteinemia are significant risk factors for the development of accelerated atherosclerosis in patients undergoing regular hemodialysis. These risk factors block the activity of the enzymes dimethyl-diamino-hydrolase - DDHA (Dimethyl-Diamino-Hydrolase) in the endothelial cells of arterial blood vessels, which breaks down asymmetric dimethylarginine - ADMA (Asymmetric Dimethylarginine) to L-citrulline and methionine. Asymmetric dimethylarginine is the most important endogenous blocker of nitric oxide synthase - NO (Nitrogen Oxide), and reduced production of nitric oxide in endothelial cells plays a key role in initiating the process of atherosclerosis (28). The process of atherosclerosis goes through several stages: increased endothelial permeability, expression of adhesion molecules on the surface of endothelial cells, adhesion and migration of leukocytes and monocytes, formation of foam cells, plaque rupture and thrombus formation. Microinflammation leads to the accumulation of neutrophils and monocytes in atherosclerotic plaque, and the release of cytokines and metalloproteinases causes rupture of the atherosclerotic plaque cap and the development of an acute coronary event (29, 30).

Anemia, erythropoietin resistance and hemoglobin variability

Microinflammation is a risk factor for the development of anemia, resistance to the action of erythropoietin, as well as for the variability of hemoglobin in patients on hemodialysis. The pathophysiological mechanisms of the development of anemia due to microinflammation can be divided into two groups: hepcidin-dependent mechanisms and hepcidin-independent mechanisms. Microinflammation (interleukin-6) stimulates the synthesis of hepcides in liver cells. Hepcidin prevents the release of iron from the cells of the reticuloendothelial system in the liver and spleen and causes a functional lack of iron (reduced amount of iron available for erythropoiesis in the bone marrow). Mechanisms independent of hepcidin include: decreased production of endogenous erythropoietin (IL-1 β , TNF α), blocking the proliferation and differentiation of erythrocyte lineage precursor cells in the bone marrow (TNF α , INF γ) and shortened erythrocyte lifespan (neutrophil elastase) (31). Erythropoietin Resistance Index (ERI) is defined as the ratio of the weekly dose of erythropoietin depending on body weight and hemoglobin concentration in the blood. Resistance to the action of short-

acting erythropoietins exists if the resistance index - $ERI \geq 1.0$ IU/kg/week/gHb. Resistance index - $ERI \geq 0.005$ μ g/kg/week/gHb indicates resistance to the action of long-acting erythropoietins. The main risk factors for the development of erythropoietin resistance include: uremic toxins, microinflammation, oxidative stress, iron deficiency, vitamin D deficiency, uncontrolled secondary hyperparathyroidism, excessive hydration, vitamin B12 and folic acid deficiency. The results of clinical trials show that the concentration of CRP in serum ≥ 20 mg/L, tumor necrosis factor - $TNF\alpha \geq 2$ ng/mL and interleukin 6 - $IL-6 \geq 40$ ng/mL indicates the existence of resistance to the action of erythropoietin in patients who are treated with regular hemodialysis (31).

Hemoglobin variability is a risk factor for adverse outcomes in patients treated with regular hemodialysis. It is defined as an oscillation of the hemoglobin concentration in the blood over a period of 8 weeks, with an amplitude greater than 15 g/L from the set target hemoglobin values (hemoglobin oscillation greater than 15 g/L from the equilibrium point with a return back to the same point during the period of at least 8 weeks). Factors that cause hemoglobin variability can be divided into three groups. The first group consists of drug-related factors (drugs), which include: pharmacokinetic characteristics of erythropoietin, bioavailability and route of administration of erythropoietin (s.c. or i.v.). Factors related to the patient include acute and chronic comorbidities: microinflammation, malnutrition, vitamin D deficiency, secondary hyperparathyroidism. The third group consists of factors related to treatment protocols and costs (refund policy) (32). The strategy to prevent the development of variability includes: more frequent monitoring of hemoglobin concentration in the blood (weekly or biweekly), gradual change of erythropoietin dose ($\pm 25\%$ of the initial dose), preventive increase of erythropoietin dose (inflammatory conditions), optimal microinflammation control, fast and effective treatment of infection, rapid and effective treatment of gastrointestinal bleeding, optimal control of secondary hyperparathyroidism, erythropoietin and iron dosage compliance, erythropoietin change, and individualization of anemia treatment (32).

Malnutrition: loss of energy due to lack of protein

Malnutrition is a risk factor for an unfavorable outcome in patients treated with regular hemodialysis. The two main pathophysiological mechanisms of malnutrition due to protein deficiency are: reduced dietary protein intake and increased catabolism of deposited proteins. Reduced dietary protein intake is a consequence of loss of appetite and reduced absorption of nutrients from the gastrointestinal tract. Increased protein catabolism in hemodialysis patients occurs due to microinflammation, oxidative stress, metabolic acidosis, insulin resistance, and testosterone deficiency (33, 34). In hemodialysis patients, dietary protein intake should be ≥ 1.2 g/kg/day and energy intake 35 kcal/kg/day. Oral Nutrition Supplementation (OSN) provides additional protein intake of 0.3-0.4 g/kg/day and energy of 10 kcal/kg/day. In patients on hemodialysis with proven malnutrition, in whom the spontaneous intake of protein is less than 0.8 g/kg/day and

energy is less than 20 kcal/kg/day, intradialysis parenteral nutrition - IDPN (Intradialytic Parenteral Nutrition) is indicated. The commercial bag contains a mixture of amino acids, glucose and lipid emulsions (1 kcal/mL, amino acids 40-60 g/L), administered in the form of IV infusion through the venous line of extracorporeal circulation, 15 minutes after the start of the dialysis session, at a maximum rate of 250 mL/h. It can provide 1000 kcal and 50 g of amino acids during a single hemodialysis session (33, 34).

Diagnosis of PEW includes four categories of clinical criteria: biochemical criteria, body mass, muscle mass, and protein and energy intake. Biochemical criteria include: serum albumin concentration less than 38 g/L, prealbumin concentration less than 0.30 g/L, serum cholesterol concentration less than 2.6 mmol/L (< 100 mg/dL). The body weight category includes the following clinical criteria: body mass index - BMI less than 23 kg/m², unintentional weight loss $\geq 5\%$ over three months or $\geq 10\%$ over 6 months, total body fat percentage less than 10%. Clinical criteria for assessing muscle mass include: unintentional decrease in muscle mass $\geq 5\%$ over 3 months or $\geq 10\%$ over six months, decreased upper arm muscle volume - MAMC by 10% compared to reference values (Mid-Arm Muscle Circumference) and the kinetics/creatinine index - SCI (Simplified Creatinine Index). The category of dietary intake include: unintentionally low protein intake less than 0.8 g/kg/day for at least two months for patients undergoing hemodialysis and less than 0.6 g/kg/day for patients suffering from chronic kidney disease stage CKD 3b-5, as well as unduly low energy intake, less than 25 kcal/kg/day for at least two months. For the diagnosis of protein deficiency malnutrition (PEW), at least three categories and at least one test result in each of the selected categories must be positive. For the diagnosis of protein deficiency malnutrition (PEW), at least three categories and at least one test result in each of the selected categories must be positive. Each criterion should be documented three times, preferably 2-4 weeks apart (33, 34).

Amyloidosis associated with dialysis

Hemodialysis-related amyloidosis occurs as a consequence of β_2 -microglobulin accumulation. In hemodialysis patients, microinflammation and metabolic acidosis promote increased β_2 -microglobulin production. In contact with other biological molecules (glycosaminoglycans, proteoglycans) conformational changes of β_2 -microglobulin occur, amyloid fibers are formed, and their deposition leads to bone and joint disorders, carpal tunnel syndrome (compression of the median tunnel) and carpal tunnel. formation of cystic formations in the bones. In patients with carpal tunnel syndrome, as a consequence of shortening of the flexor tendons of the fingers, a characteristic "guitar sign" appears. Post-dilution online hemodiafiltration and extended hemodialysis, which enable the efficient removal of β_2 -microglobulin from the patient's serum, play a key role in preventing the development and progression of hemodialysis-related amyloidosis. According to the recommendations of the JSN (Japanese Society of Nephrology), the target predialysis concentration of β_2 -

microglobulin in the serum should be less than 30 mg/L (ideally less than 25 mg/L) (35).

Prevention and treatment of microinflammation

Postdilution online hemodiafiltration - OL-HDF

Postdilution online hemodiafiltration is a method to replace kidney function that effectively removes uremic toxins of middle molecular weight in the range of 0.5-60 kDa. Studies show that it reduces microinflammation, oxidative stress, malnutrition due to protein deficiency, resistance to the action of erythropoietin and the development of accelerated atherosclerosis (36-41). High-volume postdilution online hemodiafiltration ($V_{\text{conv}} = 22\text{-}30$ liters per session) prevents the development of atherosclerotic cardiovascular diseases, reduces the risk of cardiovascular mortality and improves the quality of life of patients with end-stage chronic kidney disease (42-47). For optimal control of oxidative stress and microinflammation, high-flux hemodialysis and postdilution online hemodiafiltration with dialysis membranes coated with vitamin E are used (48-50).

The efficiency of postdilution online hemodiafiltration depends on the total convective volume - V_{conv} . The target total convective volume should be - $V_{\text{conv}} = 22\text{-}30$ liters per session. It depends on the rate of blood flow through the arteriovenous fistula ($Q_{\text{avf}} \geq 600$ mL/min), the rate of blood flow ($Q_{\text{b}} \geq 350$ mL/min) and the characteristics of the dialyzer. The main characteristics of dialyzers used for postdilution online hemodiafiltration are: high ultrafiltration coefficient ($K_{\text{uf}} > 40$ mL/h x mmHg), sieving coefficient for β_2 -microglobulin greater than 0.60, sieving coefficient for albumin less than 0.01 (albumin loss per session less than 4.0 g), capillary density greater than 11,000 per cross-sectional area of the dialyzer allows the flow of dialysis solution - $Q_{\text{d}} = 500$ mL/min, the inner diameter of the dialyzer capillaries greater than 200 μm . Dialyzers with dialysis membranes with an area of ≥ 2.0 m² should be used to optimize the filtration fraction in postdilution online hemodiafiltration (51, 52). For postdilution online hemodiafiltration, the maximum conductivity of water from the reverse osmosis system should be up to 5 $\mu\text{S/cm}$. Ultrapure dialysis solution (bacterial concentration < 0.1 CFU/mL, endotoxin concentration < 0.03 EU/mL) and sterile substitution solution (bacterial concentration $< 10\text{-}6$ CFU/mL, endotoxin concentration < 0.03 EU/mL (51, 52).

Extended hemodialysis - MCO hemodialysis

Extended hemodialysis is a method to replace kidney function that effectively removes uremic toxins of medium molecular weight, including proinflammatory cytokines, by a diffusion process and an internal filtration process. With an MCO membrane of 2.0 m², the internal filtration is high and amounts to 30-50 mL/min. Less than 4.0 g/4h is lost during a single session of extended MCO hemodialysis, which is of great importance in order to prevent malnutrition due to protein loss. It reduces microinflammation, oxidative stress, malnutrition due to protein deficiency, resistance to the

action of erythropoietin and prevents the development of accelerated atherosclerosis (53-57).

Optimization of diffusion and convective transport capacity in MCO dialysis membrane depends on blood flow rate ($Q_{\text{b}} \geq 300$ mL/min), net ultrafiltration flow rate (Q_{nuf}), internal filtration flow rate, single session duration and dialyzer characteristics. Internal filtration depends on the membrane ultrafiltration coefficient, the internal diameter of capillary fibers (< 200 μm), the net ultrafiltration flow rate and the sieving coefficient for individual uremic toxins. It increases in proportion to the strength of blood flow and the area of the MCO membrane. High internal filtration and increased MCO membrane sieving capacity enable high clearance of middle molecular weight uremic toxins. The target spKt/V index for a single session of extended MCO hemodialysis should be ≥ 1.20 (53-57).

Adsorptive hemodialysis - PMMA hemodialysis

Adsorptive hemodialysis is a method for replacing kidney function that effectively removes uremic toxins of medium and large molecular weight, as well as uremic toxins that bind in a high percentage to plasma proteins - PBUT (Protein-Bound Uremic Toxins). It combines diffusion, convection and adsorption. PMMA (Polymethyl Methacrylate) dialysis membranes have a high adsorption capacity of β_2 -microglobulin, proinflammatory cytokines (IL-6, IL-8, TNF α , HMGB-1), free light chains of monoclonal immunoglobulins and uremic toxins that in high percentage bind to plasma proteins (indoxyl sulfate, p-cresyl sulfate). Clinical studies show that adsorptive hemodialysis reduces microinflammation (removes proinflammatory cytokines), prevents malnutrition and muscle loss, significantly reduces uremic itching and the development of atherosclerotic cardiovascular diseases in the population of patients treated with regular hemodialysis (58-60). Optimization of diffusion capacity, convective transport and adsorption capacity of PMMA dialysis membrane depends on blood flow rate ($Q_{\text{b}} \geq 300$ mL/min), dialysate flow rate ($Q_{\text{d}} \geq 500$ mL/min), net ultrafiltration flow rate (Q_{nuf}), duration of individual sessions and characteristics of the dialyzer: inner diameter of capillary fibers of 200 μm , membrane wall thickness of 30 μm . The target spKt/V index for a single session of adsorptive PMMA hemodialysis should be ≥ 1.20 (58-60).

CONCLUSION

Microinflammation is a risk factor for an unfavorable outcome in patients treated with regular hemodialysis. Its prevalence in the final stage of chronic kidney disease is 30-50%. Postdilution *online* hemodiafiltration, extended and adsorptive hemodialysis prevent the development of microinflammation. Optimal control of microinflammation reduces the risk of accelerated atherosclerosis, malnutrition, resistance to the action of erythropoietin, improves the quality of life and reduces the rate of cardiovascular morbidity and mortality in patients treated with regular hemodialysis.

ACKNOWLEDGEMENTS

The authors would like to express their deepest gratitude to the Ministry of Education, Science and Technological Development of the Republic of Serbia for Grant N0175014 and also to the Faculty of Medical Sciences University of Kragujevac for their Junior Project grants N002/19 and N022/20 from which the funds were used as one of the sources to financially support this paper.

CONFLICT OF INTEREST

The authors declare no financial or commercial conflict of interest.

REFERENCES

1. Cozzolino M, Mangano M, Stucchi A, Ciceri P, Conte F, Galassi A. Cardiovascular disease in dialysis patients. *Nephrol Dial Transplant* 2018; 33(1):28-34. Doi: 10.1093/ndt/gfy174.
2. Escoli R, Carvalho MJ, Cabrita A, Rodrigues A. Diastolic Dysfunction, an Underestimated New Challenge in Dialysis. *Ther Apher Dial* 2019; 23(2): 108-17. Doi: 10.1111/1744-9987.12756.
3. Ahmadmehrabi S, Tang WHW. Hemodialysis-induced Cardiovascular Disease. *Semin Dial* 2018; 31(3): 258-67. Doi: 10.1111/sdi.12694.
4. Genovesi S, Boriani G, Covic A, Vernooij RWM, Combe C, Burlacu A, et al. Sudden cardiac death in dialysis patients: different causes and management strategies. *Nephrol Dial Transplant* 2021; 36(3): 396-405. Doi: 10.1093/ndt/gfz182.
5. Levi A, Simard T, Glover C. Coronary Artery Disease in Patients with End-Stage Kidney Disease; Current perspective and gaps of knowledge. *Semin Dial* 2020; 33(3): 187-97. Doi: 10.1111/sdi.12886.
6. Roehm B, Gulati G, Weiner DE. Heart failure management in dialysis patients: Many treatment options with no clear evidence. *Semin Dial* 2020; 33(3): 198-208. Doi: 10.1111/sdi.12878.
7. Akchurin OM, Kaskel F. Update on Inflammation in Chronic Kidney Disease. *Blood Purif* 2015; 39(1-3): 84-92. Doi: 10.1159/000368940.
8. Wolley MJ, Hutchison CA. Large uremic toxins: an unsolved problem in end-stage kidney disease. *Nephrol Dial Transplant* 2018; 33(Suppl 3): 6-11. Doi: 10.1093/ndt/gfy179.
9. Kaesler N, Babler A, Floege J, Kramann R. Cardiac Remodeling in Chronic Kidney Disease. *Toxins* 2020; 12(3): 161. Doi: 10.3390/toxins12030161.
10. Velasquez MT, Centron P, Barrows I, Dwivedi R, Raj DS. Gut Microbiota and Cardiovascular Uremic Toxicities. *Toxins* 2018; 10(7): 287. Doi: 10.3390/toxins10070287.
11. Espi M, Koppe L, Fouque D, Thaunat O. Chronic Kidney Disease-Associated Immune Dysfunctions: Impact of Protein-Bound Uremic Retention Solutes on Immune Cells. *Toxins* 2020; 12: 300. Doi: 10.3390/toxins12050300.
12. Ronco C, Clark WR. Haemodialysis membranes. *Nat Rev Nephrol* 2018; 14(6): 394-410. Doi: 10.1038/s41581-018-0002-x.
13. Haroon S, Davenport A. Choosing a dialyzer: What clinicians need to know. *Hemodialysis Int* 2018; 22(Suppl 2): 65-74. Doi: 10.1111/hdi.12702.
14. Kohlova M, Amorim CG, Araujo A, Santos-Silva A, Solich P, Montenegro MCBS. The biocompatibility and bioactivity of hemodialysis membranes: their impact in end-stage renal disease. *Int J Artif Organs* 2019; 22(1): 14-28. Doi: 10.1007/s10047-018-1059-9.
15. Chen DP, Flythe JE. Dialysis-associated allergic reactions during continuous renal replacement therapy and hemodialysis: A case report. *Hemodialysis Int* 2020; 24(1): 5-9. Doi: 10.1111/hdi.12801.
16. Martin-Navarro J, Esteras R, Castillo E, Carriazo S, Fernandez-Prado R, Gracia-Iguacel C, et al. Reactions to Synthetic Membranes Dialyzers: Is there an Increase in Incidence? *Kidney Blood Press Res* 2019; 44(5): 907-14. Doi: 10.1159/000501035.
17. Glorieux G, Neirynck N, Veys N, Vanholder R. Dialysis water and fluid purity: more than endotoxin. *Nephrol Dial Transplant* 2012; 27(11): 4010-21. Doi: 10.1093/ndt/gfs306.
18. Kraut JA, Madias NE. Metabolic Acidosis of CKD: An Update. *Am J Kidney Dis* 2016; 67(2): 307-17. Doi: 10.1053/j.ajkd.2015.08.028.
19. Raphael KL. Metabolic Acidosis in CKD: Core Curriculum 2019. *Am J Kidney Dis* 2019; 74(2): 263-75. Doi: 10.1053/j.ajkd.2019.01.036.
20. 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. Doi: 10.1111/sdi.12745.
21. Yang SK, Xiao L, Xu B, Xu XX, You F, 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. Doi: 10.3109/0886022X.2014.890858.
22. Jovanovich A, Isakova T, Stubbs J. Microbiome and Cardiovascular Disease in CKD. *Clin J Am Soc Nephrol* 2018; 13(10): 1598-604. Doi: 10.2215/CJN.12691117.
23. Van der Sande FM, Van de Wal-Visscher ER, Suard S, Moissi U, Kooman JP. Using Bioimpedance Spectroscopy to Assess Volume Status in Dialysis Patients. *Blood Purif* 2020; 49(1-2): 178-84. Doi: 10.1159/000504079.
24. Dekker MJE, Van der Sande FM, Van den Berghe F, Leunissen KML, Kooman JP. Fluid Overload and Inflammation Axis. *Blood Purif* 2018; 45(1-3): 159-65. Doi: 10.1159/000485153.
25. Dekker MJE, Konings C, Canaud B, Usvyat L, Kotanko P, Kooman JP. Interactions Between Malnutrition, Inflammation, and Fluid Overload and Their Associations With Survival in Prevalent Hemodialysis

- Patients. *J Ren Nutrition* 2018; 28(6): 435-44. Doi: 10.1053/j.jrn.2018.06.005.
26. Dekker MJE, Marcelli D, Canaud BJ, Carioni P, Wang Y, Grassmann A, et al. Impact of fluid status and inflammation and their interaction on survival: a study in an international hemodialysis patient cohort. *Kidney Int* 2017; 91(5): 1214-23. Doi: 10.1016/j.kint.2016.12.008.
 27. Icardi A, Paoletti E, De Nicola L, Mazzaferro S, Russo R, Cozzolino M. Renal anemia and EPO hyporesponsiveness associated with vitamin D deficiency: the potential role of inflammation. *Nephrol Dial Transplant* 2013; 28(7): 1672-9. Doi: 10.1093/ndt/gft021.
 28. Tain YL, Hsu CN. Toxic Dimethylarginines: Asymmetric Dimethylarginine (ADMA) and Symmetric Dimethylarginine (SDMA). *Toxins* 2017; 9(3): 92. Doi: 10.3390/toxins9030092.
 29. Weiss G, Ganz T, Goodnough LT. Anemia of inflammation. *Blood* 2019; 133(1): 40-50. Doi: 10.1182/blood-2018-06-856500.
 30. Szeto CC, McIntyre CW, Li PKT. Circulating Bacterial Fragments as Cardiovascular Risk Factors in CKD. *J Am Soc Nephrol* 2018; 29(6): 1601-8. Doi: 10.1681/ASN.2018010068.
 31. Gluba-Brzozka A, Franczyk B, Olszewski R, Rysz J. The Influence of Inflammation on Anemia in CKD Patients *Int J Mol Sci* 2020; 21(3): 725. Doi: 10.3390/ijms21030725.
 32. Kalantar-Zadeh K, Aronoff GR. Hemoglobin Variability in Anemia of Chronic Kidney Disease. *J. Am Soc Nephrol* 2009; 20(3): 479-87. Doi: 10.1681/ASN.2007070728.
 33. Ikizler TA, Burrowes JD, Byham-Gray LD, Campbell KL, Carrero JJ, Chan W, et al. KDOQI clinical practice guidelines for nutrition in CKD: 2020 Update. *Am J Kidney Dis* 2020; 76(3 Suppl 1): 1-107. Doi: 10.1053/j.ajkd.2020.05.006.
 34. Sabatino A, Piotti G, Cosola C, Gandolfini I, Kooman JP, Ficcadori E. Dietary protein and nutritional supplements in conventional hemodialysis. *Semin Dial* 2018; 31(6): 583-91. Doi: 10.1111/sdi.12730.
 35. Kaneko S, Yamagata K. Hemodialysis-related amyloidosis: Is it still relevant? *Semin Dial* 2018; 31(6): 612-8. Doi: 10.1111/sdi.12720.
 36. Wolley M, Jardine M, Hutchison CA. Exploring the Clinical Relevance of Providing Increased Removal of Large Middle Molecules. *Clin J Am Soc Nephrol* 2018; 13(5): 805-14. Doi: 10.2215/CJN.12631117.
 37. Canaud B, Vienken J, Ash S, Ward R. Hemodiafiltration to Address Unmet Medical Needs ESKD Patients. *Clin J Am Soc Nephrol* 2018; 13(9): 1435-43.
 38. Nenadovic M, Jacovic S, Nikolic A, Kostovic M, Draskovic B, Jovanovic M, Nikolic T, Petrovic D. Postdilution online hemodiafiltration: basic principles and clinical significance. *Ser J Exp Clin Res* 2020; Doi: 10.2478/sjecd-2020-0055.
 39. Nenadovic M, Jacovic S, Nikolic A, Kostovic M, Draskovic B, Jovanovic M, Nikolic T, Petrovic D. Assessment of the influence of postdilution online hemodiafiltration on the rate of removal of middle molecular weight uremic toxins. *Ser J Exp Clin Res* 2021; Doi: 10.2478/sjecd-2021-0005.
 40. Nenadovic M, Nikolic A, Kostovic M, Draskovic B, Jovanovic M, Nikolic T, Petrovic D. Poredjenje efikasnosti uklanjanja uremijskih toksina srednje molekulske mase izmedju visokopropusne hemodijalize i postdilucione online hemodijafiltracije. *Med Cas* 2021; 55(1): 7-17. Doi: 10.5937/mckg55-31062.
 41. Nenadovic M, Petrovic D, Trbojevic-Stankovic J. Beta-2-microglobulin removal with postdilution online hemodiafiltration - comparison of three different dialysis membranes. *Srp Arh Celok Lek* 2021; 149(7-8): 422-7. Doi: 10.2298/SARH210329048N.
 42. Marcelli D, Scholz C, Ponce P, Sousa T, Kopperschmidt P, Grassmann A, et al. High-Volume Postdilution Hemodiafiltration Is a Feasible Option in Routine Clinical Practice. *Artif Organs* 2015; 39(2): 142-9. Doi: 10.1111/aor.12345.
 43. Marcelli D, Kopperschmidt P, Bayh I, Jirka T, Merello JJ, Ponce P, et al. Modifiable factors associated with achievement of high-volume post-dilution hemodiafiltration: results from an international study. *Int J Artif Organs* 2015; 38(5): 244-50. Doi: 10.5301/ijao.5000414.
 44. De Roij van Zuijdewijn CLM, Chapdelaine I, Nube MJ, Blankestijn PJ, Bots ML, Konings CJAM, Hovinga TKK, et al. Achieving high convection volumes in postdilution online hemodiafiltration: a prospective multicenter study. *Clin Kidney J* 2017; 10(6): 804-12. Doi: 10.1093/ckj/sfw140.
 45. Chapdelaine I, De Roij van Zuijdewijn CLM, Mostovaya IM, Levesque R, Davenport A, Blankestijn PJ, et al. Optimization of the convection volume in online postdilution haemodiafiltration: practical and technical issues. *Clin Kidney J* 2015; 8(2): 191-8. Doi: 10.1093/ckj/sfv003.
 46. Panichi V, Scatena A, Rosati A, Giusti R, Ferro G, Malagnino E, et al. High-volume online haemodiafiltration improves erythropoiesis-stimulating agent (ESA) resistance in comparison with low-flux bicarbonate dialysis: results of the REDERT study. *Nephrol Dial Transplant* 2015; 30(4): 682-9. Doi: 10.1093/ndt/gfu345.
 47. Rosati A, Ravaglia F, Panichi V. Improving Erythropoiesis Stimulating Agent Hyporesponsiveness in Hemodialysis Patients: The Role of Heparin and Hemodiafiltration Online. *Blood Purif* 2018; 45(1-3): 139-46. Doi: 10.1159/000485314.
 48. Locatelli F, Andrulli S, Vigano SM, Concetti M, Urbini S, Giacchino F, et al. Evaluation of the Impact of a New Synthetic Vitamin E-Bonded Membrane on the Hypo-Responsiveness to the Erythropoietin Therapy in Hemodialysis Patients: A Multicenter Study. *Blood Purif* 2017; 43(4): 338-45. Doi: 10.1159/000453442.
 49. Antic S, Draginic N, Pilcevic D, Zivkovic V, Srejsovic I, Jeremic N, Petrovic D, Jakovljevic V. The influence of vitamin E coated dialysis membrane on oxidative stress

- during the single session of online hemodiafiltration. *Vojnosanit Pregl* 2021; 78(5): 511-8. Doi: 10.2298/VSP190730097A.
50. Kiaii M, Aritomi M, Nagase M, Farah M, Jung B. Clinical evaluation of performance, biocompatibility, and safety of vitamin E-bonded polysulfone membrane hemodialyzer compared to non-vitamin E-bonded hemodialyzer. *J Artif Org* 2019; 22: 307-15. Doi: 10.1007/s10047-019-01110-w.
51. Maduell F. Hemodiafiltration versus conventional hemodialysis: Should “convencional” be redefined? *Semin Dial* 2018; 31(6): 625-32. Doi: 10.1111/sdi.12715.
52. Guedes M, Dambiski AC, Canhada S, Barra ABL, Poli-De-Figueiredo CE, Cuvello Neto AL, et al. Achieving high convective volume in hemodiafiltration: Lessons learned after successful implementation in the HDFit trial. *Hemodialysis Int* 2021; 25(1): 50-9. Doi: 10.1111/hdi.12891.
53. Florens N, Juillard L. Expanded haemodialysis: news from the field. *Nephrol Dial Transplant* 2018; 33(Suppl 3): 48-52. Doi: 10.1093/ndt/gfy203.
54. Ronco C, Marchionna N, Brendolan A, Neri M, Lorenzin A, Rueda AJM. Expanded haemodialysis: from operational mechanism to clinical results. *Nephrol Dial Transplant* 2018; 33(Suppl 3): 41-7. Doi: 10.1159/000489993.
55. Lorenzin A, Neri M, Lupi A, Todesco M, Santimaria M, Alghisi A, et al. Quantification of Internal Filtration in Hollow Fiber Hemodialyzers with Medium Cut-Off Membrane. *Blood Purif* 2018; 46(3): 196-204. Doi: 10.1159/000489993.
56. Nenadovic M, Nikolic A, Kostovic M, Draskovic B, Jovanovic M, Nikolic T, Petrovic D. Assessment of the influence of expanded hemodialysis on the rate of removal of middle molecular weight uremic toxins. *Med Cas* 2020; 54(3): 96-104. Doi: 10.5937/mckg54-30496.
57. Lim JH, Jeon Y, Yook JM, Choi SY, Jung HY, Choi JY, et al. Medium cut-off dialyzer improves erythropoiesis stimulating agent resistance in a hepcidin-independent manner in maintenance hemodialysis patients: results from a randomized controlled trial. *Rep Sci* 2020; 10(1): 16062. Doi: 10.1038/s41598-020-73124-x.
58. Masakane I, Esashi S, Yoshida A, Chida T, Fujieda H, Ueno Y, et al. A new polymethylmethacrylate membrane improves the membrane adhesion of blood components and clinical Efficacy. *Ren Repl Ther* 2017; 3: 32. Doi: 10.1186/s41100-017-0112-0.
59. Van Gelder MK, Middel IR, Vernooij RWM, Bots ML, Verhaar MC, Masereeuw R, et al. Protein-Bound Uremic Toxins in Hemodialysis Patients Relate to Residual Kidney Function, Are Not Influenced by Convective Transport, and Do Not Relate to Outcome. *Toxins* 2020; 12(4): 234. Doi: 10.3390/toxins12040234.
60. Maduell F, Broseta JJ, Rodriguez-Espinosa D, Hermida-Lama E, Rodas LM, Gomez M, et al. Evaluation and comparison of polysulfone TS-UL and PMMA NF-U dialyzers versus expanded hemodialysis and postdilution hemodiafiltration. *Artif Organs* 2021; Doi: 10.1111/aor.13968.

