NON-TRADITIONAL RISK FACTORS FOR DEVELOPMENT OF CARDIOVASCULAR COMPLICATIONS IN HAEMODIALYSIS PATIENTS

Dejan Petrović1, Nikola Jagić2, Vladimir Miloradović3, Biljana Stojimirović4

1Clinic for Urology and Nephrology, Centre for Nephrology and Dialysis, Clinical Centre "Kragujevac", 2Center for Radiology Diagnostics, Department for Interventional Radiology, Clinical Centre "Kragujevac", 3Clinic for Internal Medicine, Centre for Cardiology, Clinical Centre "Kragujevac", Kragujevac, 4Institut for Urology and Nephrology, Clinic for Nephrology, Clinical Centre of Serbia, Belgrade

ABSTRACT
Cardiovascular diseases are a leading cause of death in patients treated with haemodialysis. These patients are exposed to traditional and non-traditional risk factors for cardiovascular complications. Non-traditional risk factors are consequences of uremic milieu, but these can also be linked to the technique of dialysis itself. Non-traditional risk factors include oxidative stress, microinflammation, malnutrition, secondary hyperparathyroidism, anaemia, hyperhomocysteinaemia, retention of sodium and water and increase of blood flow through the vascular access for haemodialysis. These risk factors are implicated in left ventricle hypertrophy and accelerate atherosclerosis. In addition, they increase cardiovascular morbidity and mortality in these patients. Aggressive cardiovascular risk factor modification can significantly improve cardiovascular outcome in patients treated with haemodialysis.

Key words: cardiovascular risk factors, microinflammation, malnutrition, haemodialysis.

INTRODUCTION
Cardiovascular diseases are a leading cause of mortality in patients treated with haemodialysis (1, 2). Traditional and non-traditional risk factors for cardiovascular complications in haemodialysis patients are numerous. Traditional risk factors include high blood pressure, lipid metabolism disorders, diabetes mellitus, obesity, cigarette smoking and reduced physical activity. Non-traditional risk factors can be metabolic (microinflammation, hyperhomocysteinaemia, high concentration of asymmetric dimethylarginine, oxidative stress, malnutrition, secondary hyperparathyroidism) or haemodynamic (anaemia, sodium and water retention and high blood flow through the vascular access for haemodialysis) (table 1) (3-5). Timely detection of risk factors and adequate therapy can significantly reduce cardiovascular morbidity and mortality in patients treated with haemodialysis (3-5).

Table 1: Risk factors for development of cardiovascular complications in dialysis patients

<table>
<thead>
<tr>
<th>CARDIOVASCULAR RISK FACTORS</th>
<th>TRADICIONAL</th>
<th>METABOLIC</th>
<th>HEMODYNAMIC</th>
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<tbody>
<tr>
<td>Hypertension</td>
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<td>Hyperlipidaemia</td>
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<td>Diabetes mellitus</td>
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<td>Cigarette smoking</td>
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<td>Obesity</td>
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<td>Reduced physical activity</td>
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Qav - flow through vascular haemodialysis access

SAŽETAK
Kardiovaskularne bolesti su vodeći uzrok smrti bolesnika koji se leće hemodijalizom. Ovi bolesnici su izloženi tradicionalnim i netradicionalnim faktorim rizika za razvoj kardiovaskularnih komplikacija. Netradicionalni faktori rizika su posledica uremijskog miljea, a mogu biti povezani i sa samom tehnikom dijalize. U netradicionalne faktore rizika spadaju mikroinfl amacija, hiperhomocisteinemija, povećana koncentracija asimetričnog dimetilarginina, oksidativni stres, malnutricija, sekundarni hiperparatireoidizam, anemija, reten- cija Na+ i H2O i povećan protok krv kroz vaskularni pristup za hemodijalizu. Pomenuti faktori rizika uzrokuju hipertrofi ju leve komore i ubrzanju aterosklerozu, a to za posledicu ima povećan kardiovaskularni morbiditet i mortalitet ovih bole- snika. Uticajem na faktore rizika za razvoj kardiovaskularnih komplikacija, može se značajno popraviti kardiovaskularni ishod bolesnika koji se leće hemodijalizom.

Ključne reči: faktori kardiovaskularnog rizika, mikroinfl a- macija, malnutricija, hemodijaliza
METABOLIC RISK FACTORS

Microinflammation
Microinflammation is a risk factor for atherosclerotic cardiovascular complications in patients treated with haemodialysis (6, 7). The normal concentration of C-reactive protein (CRP) in plasma is ≤ 5 mg/L, and concentrations of CRP > 10 mg/L indicate the presence of microinflammation and an elevated risk for the development of cardiovascular complications (6, 7). Microinflammation is present in 30-50% of patients. The quality of water for dialysis, biocompatibility of the dialysis membrane and vascular access for haemodialysis are all key factors in the provocation and maintenance of low degree chronic microinflammation in these patients (6-8). Microinflammation plays an important role in the process of atherosclerosis, plaque formation and rupture (6-8). Haemodialysis patients with CRP concentration > 15.8 mg/L have a 2.4-fold greater risk for cardiovascular mortality in comparison to patients with CRP < 3.3 mg/L (9). Patients with plasma CRP concentration > 11.5 mg/L have a highly statistically significant decrease in survival in comparison with patients treated with haemodialysis with a CRP concentration < 2.6 mg/L (10). Notably, bicarbonate haemodialysis with polysulfonic biocompatible membrane along with the use of ultrapure haemodialysis solution contributes to a decrease in CRP levels (11).

Hyperhomocysteinaemia
Hyperhomocysteinaemia is a risk factor for atherosclerosis and cardiovascular complications in haemodialysis patients (12-14). It is defined as a plasma homocysteine concentration ≥15 µmol/L and is present in over 80% of patients treated with haemodialysis (12-14). It is as a consequence of the decreased activity of key enzymes involved in homocysteine metabolism (methionine synthase, N5,N10-methyl tetrahydrofolate reductase, cystation β-synthase, betain-homocystein methyltransferase) (12-14). Hyperhomocysteinaemia blocks the degradation of asymmetric dimethylarginine (ADMA), contributes to the accumulation of ADMA in blood vessel endothelial cells and triggers atherosclerosis (scheme 1) (12-14). The concentration of whole serum homocystein - tHcy is an independent predictor of cardiovascular mortality in patients treated with regular haemodialysis. Patients treated with haemodialysis who have plasma homocystein concentrations ≥ 37.8 µmol/L exhibit an 8.2-fold greater risk for cardiovascular mortality in comparison with patients who have serum homocystein levels ≤ 22.9 µmol/L (15). Use of folan, vitamin B6, vitamin B12 and active metabolites of folic acid significantly contributes to decreased serum homocystein concentrations in patients treated with haemodialysis (16).

High concentration of asymmetric dimethylarginine
A high concentration of asymmetric dimethylarginine (ADMA) is a risk factor for cardiovascular complications in haemodialysis patients. It is defined as an ADMA concentration > 2.2 µmol/L and is due to decreased activity of the enzyme dimethylarginine dimethylhydrolase (DDHA) (17, 18). Microinflammation, diabetes mellitus, hyperhomocysteinaemia and oxidative stress significantly decrease the activity of this enzyme and increase the concentration of ADMA. ADMA blocks the production of nitrous oxide (NO) in endothelial cells and contributes to the development of atherosclerosis (scheme 1) (17, 18). Asymmetric dimethylarginine is an independent risk factor for left ventricle hypertrophy and a predictor of poor outcome in patients treated with haemodialysis (19). Increases in serum ADMA are accompanied by a 26% increase in overall mortality risk per µmol increase (20). Control of blood pressure, glycaemia, L-arginine and antioxidants improves the activity of DDHA and decreases the serum ADMA concentration (17-20).

Oxidative stress
Augmentation of oxidative stress is a risk factor for development of atherosclerotic cardiovascular complications in patients on haemodialysis (21). Oxidative stress and elevated oxLDL concentration block DDHA activity and decrease ADMA degradation. Accumulation of ADMA perturbs the function of the L-arginine/NO system in endothelial cells, resulting in decreased NO elaboration and the development of atherosclerosis (scheme 1) (21). Use of L-arginine, vitamin E and N-acetylcysteine significantly contributes to decreasing oxidative stress and decreased risk of cardiovascular complications in patients treated with haemodialysis (22).

Malnutrition
In patients treated with haemodialysis, malnutrition due to insufficient protein consumption shows that there is microinflammation (23). Syndrome of malnutrition-inflammation (MICS) occurs due to appetite loss, insufficient nutrition, increased nutrient loss during haemodialysis, presence of uremic toxins, hypercatabolism produced by co-morbidities (diabetes mellitus, infection, sepsis, congestive heart failure), increased oxidative stress, and use of biocompatible dialysis membranes and conventional haemodialysis solution (23). As a consequence, inadequate response to erythropoietin, accelerated atherosclerosis and greater cardiovascular morbidity and mortality occur in patients treated with haemodialysis (23). Daily energy intake of 45 kcal/kgbmday and protein intake of 1.5 g/kgbmday lead to body mass growth and an increase in the concentration of serum albumin in patients treated with haemodialysis (23). Intradialysis parenteral nutrition (IDPN) along with appetite-stimulating medicines (megestrol acetate, L-carnitin) significantly improves nutritional status and outcomes in haemodialysis patients (23). Optimisation of dialysis treatment (with biocompatible dialysis membrane, dialysators with vitamin E, and an ultrapure solution for haemodialysis) also contributes to better outcomes in haemodialysis patients (23).
Secondary hyperparathyroidism

Secondary hyperparathyroidism (SHTPH) frequently occurs in patients treated with regular haemodialysis. It is due to the decreased production of active metabolites of vitamin D3, hypocalcaemia and hyperphosphataemia, and its main clinical consequences are renal osteodystrophy with bone hypermetabolism, vascular and valvular calcifications and cardiovascular complications (24). Calcifications may occur in the tunica intima (atherosclerotic plaques), tunica media of the coronary vessels or in heart valves (24). Calcifications in the intima of the coronary arteries cause shrinkage of their lumen and result in the inability to supply the myocardium sufficiently (ischaemia). In addition, plaque rupture can cause acute coronary syndrome. Calcifications in media make arteries harder, increase the afterload of the left ventricle and contribute to its hypertrophy. Heart valve calcifications lead to aortic and mitral valve stenosis (24). Treatment of secondary hyperparathyroidism should enable patients to reach target endpoints for parameters involved in the metabolism of calcium and phosphate [intact parathormone (iPTH) 150 - 300 pg/mL (16.5 - 33.0 mg/dL) serum calcium concentration (Ca2+) 2.10 - 2.37 mmol/L (8.4 - 9.5 mg/dL), serum phosphate concentration (PO43-) 1.13 - 1.78 mmol/L (3.5 - 5.5 mg/dL), solubility product (CaxPO4) < 4.5 mmol2/L2 (< 55 mg2/dL2)] (25). In patients treated with regular haemodialysis, monitoring of calcium and phosphate should take place once every month, and monitoring of parathormone should be done every three months (25). Phosphate intake restriction (10 mg/kg bm/day), phosphate binders without calcium, new vitamin D metabolites and calcimimetics contribute to better control of secondary hyperparathyroidism and decrease the risk of cardiovascular morbidity and mortality in patients treated with haemodialysis (scheme 2) (26-30).

HAEMODYNAMIC RISK FACTORS

Anaemia

Anaemia is an independent risk factor for left ventricle hypertrophy in patients treated with haemodialysis (31). It is defined as a concentration of haemoglobin < 110 g/L and is present in over 90% of patients on haemodialysis (31, 32). Anaemia mostly comes from insufficient endogenous erythropoietin, and its main drawbacks to the cardiovascular system are decreased blood viscosity, low peripheral resistance (vasodilatation due to hypoxia), tachycardia and increased cardiac output (scheme 3) (31-35). By activation of haemodynamic adaptation mechanisms, anaemia overloads the left ventricle with excessive volume and causes its hypertrophy (31-35). Administration of erythropoietin enables patients to reach endpoint targets for haematocrit and haemoglobin (haemoglobin 110-120 g/L) and reduces left ventricle hypertrophy (36, 37).

Na+ and H2O retention

Interdialysis weight gain (IDWG) is a direct consequence of increased mineral and water intake in the interdialysis interval. IDWG is calculated from the following formula: IDWG% = [IDWG (kg)/DW (kg)] x 100%, where IDWG is interdialysis weight gain and DW is a patient’s dry weight (38). Patients with an IDWG < 3.0% have a statistically lower body mass index in comparison to patients with IDWG > 3.0% (38). Increased mineral and water intake (IDWG > 5.0%) leads to left ventricle volume over-
Scheme 2. Protocol for secondary hyperparathyroidism treatment in dialysis patients

Modified according to reference [28].

Conversion units: calcium 2.1 mmol/l = 8.4 mg/dl; calcium 2.4 mmol/l = 9.5 mg/dl; phosphate: 1.8 mmol/l = 5.5 mg/dl; iPTH 300 pg/ml = 31.8 pmol/l; iPTH 150 pg/ml = 15.9 pmol/l; iPTH 100 pg/ml = 10.6 pmol/l; iPTH 800 pg/ml = 84.8 pmol/l.

Scheme 3. Influence of anaemia on remodelling the cardiovascular system in dialysis patients

Modified according to reference [35].

EDRF - endotel relaxing factor
load, increased arterial pressure and left ventricle hypertrophy (38). Restriction of mineral intake (2.0 g/24h NaCl) as well as liquids in between two dialysis sessions decreases the risk of development of cardiovascular complications in dialysis patients (38).

**Increased flow through the vascular haemodialysis access**

Increased flow through the vascular haemodialysis access is a risk factor for development of cardiovascular complications (table 2) (39, 40). Normal flow through the arteriovenous fistula (AVF) is 100350 cm/s, and normal blood flow is 500 - 1000 mL/min (39, 40). Increased flow through the vascular haemodialysis access is associated with increased end diastolic diameter (EDD) and increased end diastolic left ventricle volume (EDV) (41). Blood flow through the vascular haemodialysis access (QAV > 1000 mL/min) overloads the left ventricle with excess volume and stimulates a series of adaptive processes resulting in left ventricle remodelling (scheme 4) (42, 43).

**Strategy for prevention of development of cardiovascular complications**

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<thead>
<tr>
<th>RISK FACTORS</th>
<th>DESCRIPTION</th>
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<tbody>
<tr>
<td>1.</td>
<td>Increased flow through the access - QAV &gt; 1000 mL/min</td>
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<tr>
<td>a) congestive heart failure</td>
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<tr>
<td>b) distal steal phenomenon</td>
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<tr>
<td>2.</td>
<td>Decreased flow through the access - QAV &lt; 300 mL/min</td>
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<tr>
<td>a) inadequate haemodialysis - Kt/V index &lt; 1.2</td>
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<tr>
<td>b) malnutrition - hypoalbuminaemia (albumin &lt; 35 g/l)</td>
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<tr>
<td>3.</td>
<td>Infection of vascular access</td>
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<tr>
<td>a) infectious endocarditis</td>
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<td>b) chronic microinflammation - CRP &gt; 10 mg/l</td>
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Table 2: Risk factors for the development of cardiovascular complications in dialysis patients

Determination of the most sensitive parameters for detection of patients with a high risk of development of cardiovascular complications and early detection of cardiovascular risk factors enables timely and adequate therapy. This provides for a high survival rate and better quality of life of patients with end stage renal disease (44-49).

Cardiovascular risk factor modification can significantly improve cardiovascular outcomes in dialysis patients. Strict volume arterial pressure control, adequate dialysis dose, correction of anaemia by the use of erythropoietin, using carvedilol in patients with dilative myopathy, and secondary hyperparathyroidism therapy (calcimetics in the therapy of secondary hyperparathyroidism) significantly improve cardiovascular outcomes in dialysis patients (table 3) (50, 51).

Overall cardiovascular risk in dialysis patients is the sum of traditional (TRF) and non-traditional risk factors (NTRF), uraemia-related risk factors (URRF) and dialysis technology-related risk factors (DTRRF) (52). Components of the dialysis procedure directly associated with increased risk of cardiovascular complications include the following: dialysator type (coefficient of ultrafiltration, dialysis membrane type, biocompatibility of dialysis membrane), microbiological quality of water and dialysis solutions, therapeutic modality and online monitoring (52, 53). Adequate dialysis procedure can greatly improve outcome in patients treated with regular haemodialysis (52, 53).

**REFERENCES**


