Chapter

Cardiorenal Syndrome in Patients on Renal Replacement Therapy

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Abstract

In this chapter authors discusses cardiorenal relationships in patients with renal replacement therapy (RRT) which are considered as a separate type of cardiorenal syndrome (CRS). Frequency and severity of CRS in patients on dialysis are correlated with quantity of years of the dialysis treatment; depend on quality of dialysis regimen and level of residual renal function. RRT-associated cardiac pathology are including left ventricular hypertrophy, ischemic cardiomyopathy, congestive heart failure, coronary atherosclerosis and calcinosis, severe arrhythmias. The article analyzes role of malnutrition and dialysis-induced cachexia, bio-incompatibility of dialysis membranes, oxidative stress and inflammation, arterio-venous fistula, decrease of residual renal function in the development of dialysis-induced CRS. The review examines the mechanisms of progressive myocardial ischemia induced by dialysis: myocardial stunning, hemodialysis-induced hypotension, uremic small vessel disease. Prevention of dialysis-induced CRS includes a choice of the optimal RRT method (peritoneal dialysis or hemodialysis), control of dialysis regimen, residual renal function, biocompatibility of membrane, inflammatory markers, body mass index, serum level albumin, phosphate, calcium, parathyroid hormone, fibroblast growth factor-23. Electrocardiogram, ultrasonic monitoring and coronarography reveals indications for conservative cardioprotective therapy and angioplasty interventions, including coronary artery bypass surgery and cardiac pacemaker implantation, in patients with dialysis-induced CRS.

Keywords: cardiorenal syndrome, hemodialysis, peritoneal dialysis, residual renal function, oxidative stress, malnutrition

1. Introduction

Cardiorenal syndrome (CRS) refers to the "vicious circle" of interrelated damage of the heart and kidneys, in which dysfunction of one organ complicates the dysfunction of the other, with gradual development of the cardiorenal decompensation.

C. Ronco distinguished 5 clinical types of CRS [1]:

Type 1: Acute worsening of heart function leading to kidney injury and/or dysfunction.

Type 2: Chronic abnormalities in heart function leading to kidney injury or dysfunction. This subtype refers to a more chronic state of kidney disease complicating chronic heart disease, the so-called chronic kidney disease (CKD).

Type 3: Acute worsening of kidney function leading to heart injury and/or dysfunction (acute heart failure).
Type 4: Chronic kidney disease causing cardiac overload, leading to progressive chronic cardiac dysfunction.
Type 5: Systemic condition (e.g., sepsis, vasculitis) leading to simultaneous injury and/or dysfunction of heart and kidney.

We can see the interplay of decreased glomerular filtration rate and impaired cardiac contractile function early in chronic kidney disease (CKD) worsening as renal failure increases. However, the existing classification of CRS does not consider the population of patients on renal replacement therapy (RRT), where the effect of dialysis treatment itself engages additional mechanisms of pathogenesis of cardiac pathology. Thus, the progression of cardiac dysfunction with decreasing ejection fraction reduces the effectiveness of hemodialysis (HD), while reducing the intensity of dialysis regimen and gradual loss of residual renal function speeds up the atherosclerosis and cardiomyopathy progression.

Thus, one can consider the cardiorenal relationships in patients on RRT, reflecting progression and myocardial damage in dialysis patients, as a separate type of CRS where the renal component implies end stage renal disease (ESRD) with complicating metabolic and endocrine disorders, complete loss of residual renal function, and dialysis therapy.

The features of cardiac dysfunction in patients on RRT include its widespread prevalence and severity [2]. The incidence of left ventricular myocardial hypertrophy (LVH) increases with increasing stage of CKD, reaching 90% in stages 4–5 [3]. Prevalence and severity of cardiac pathology, both coronary and non-coronary, increases rapidly in the dialysis stage of renal failure, correlating with dialysis experience. In 75–80% of patients with CKD stage 5D, secondary cardiomyopathy develops predisposing to congestive heart failure (CHF), acute coronary syndrome, or complex rhythm and conduction abnormalities. In patients on RRT, progressive atherosclerosis is associated with activation of inflammatory reactions and high frequency of protein-energy malnutrition (PEM) [4]. Thus, PEM is diagnosed in 20–50% of patients with pre-dialysis stages of CKD, increasing to 50–80% in patients on regular HD and permanent PD.

The cardiac function in patients on RRT deteriorates progressively under several pathogenetic mechanisms. These include bio-incompatibility of dialysis membranes and solutions, ineffective dialysis, PEM, dialysis hypotension, rapid decline and subsequent complete loss of residual renal function, vascular calcification, excessive shunt from arterio-venous hemodialysis fistula (AVF).

2. Bio-incompatibility of dialysis membranes, activation of oxidative stress, and inflammation

CKD in RRT is characterized by higher level of uremia and the impact of dialysis procedure itself. Despite the successes of modern hemodialysis therapy, the problem of hemodialysis membranes' bio-incompatibility is still unresolved. A key inducer of blood cell activation is dialyzer membrane material, along with the endotoxin contamination of dialysis solutions. Membrane contact with blood causes pro-inflammatory and pro-oxidant stress, thrombosis, and release of oxidative stress biomarkers, inflammatory and anti-inflammatory cytokines (IFN-γ, TNF-α, IL -1β, IL-4, IL-6, IL-10, IL-12, and IL-18), and acute phase proteins (C-reactive protein, fibrinogen) [5]. Other consequences of bio-incompatibility are complement [6] and platelet activation [7].

The oxidative events induced by extracorporeal treatment are thought to affect the concomitant pathology. Chronic inflammation, besides cardiovascular dysfunction, contributes to worsening renal anemia by reducing sensitivity to the erythropoietin-stimulating agent and shortening the life span of red blood cells [8, 9]. Also, blood leukocyte activation, oxidative stress, and mechanical factors damage the red blood cells. Leukocytes in contact with bio-incompatible dialysis membranes re-activate. The resultant leukopeniais considered a major cause of defective cellular immune response in patients on hemodialysis (HD) [10, 11]. Changes in lymphocyte phenotype (from Th1 to Th2) cause this response and excessive synthesis of pro-inflammatory cytokines [5]. Bio-incompatible membranes release pyrogens and active inflammatory mediators (histamine and bradykinin). These contribute to fever and hemodialysis-induced hypotension [12]. The latter is a key factor in residual renal function reducing in patients on regular HD [13].

Dialysate composition for peritoneal dialysis (PD) can also cause oxidative stress and inflammation [14, 15]. High concentrations of glucose and lactate, and low pH or hyperosmolality of dialysate for PD contribute to excessive production of reactive oxygen species and accumulation of oxidative damage products in the peritoneum, increasing calcification and fibrosis. The relationship between the preserved residual renal function and oxidative stress has been shown to correlate with cardiovascular risk and survival in patients on PD [14]. Given the longer preservation of residual renal function in patients on PD treatment, this method can be considered more favorable for patients with cardiovascular diseases (CVD). Also, several studies have shown a higher accumulation of oxidants and depletion of antioxidant reserves in patients on HD compared with those on PD [15, 16].

The accumulation of oxidative stress products is the highest in patients with ESRD. Peroxidizing agents oxidize unsaturated lipids [17–19] and endogenous pro-oxidants damage plasma proteins with the formation of glycation products [20–22]. Small reactive carbonyls and larger posttranslational uremic-modified proteins form many inflammatory mediators, reflecting uremic toxicity that is little dependent on the method of dialysis therapy [23]. However, all modern diffusion, convective, or mixed methods do not remove medium- and high-molecular-weight dissolved substances modified by reactive oxygen species (ROS) and reactive carbonyls effectively from blood [24–26].

Oxidative stress plays a key role in the development of cardiac dysfunction in patients on RRT. In patients with ESRD, the balance between nitric oxide (NO) and ROS is shifted toward the latter by increasing ROS production and decreasing NO availability [27]. Pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α can stimulate renin synthesis and norepinephrine secretion [28, 29]. IL-6 induces AT-1 receptors and angiotensin II-mediated ROS production in cultured rat smooth muscle cells, supporting the link between inflammation, renin-angiotensin-aldosterone system (RAAS) activation, and oxidative stress [30]. Volume overload on RRT and venous stasis are additional sources of inflammatory mediators [31, 32]. Because of intravascular overload, the vascular endothelium may be a major source of cytokine production in response to biomechanical stress [33]. Thus, the above data confirms the potential role of circulating cellular precursors of ROS and/or local agonists of ROS synthesis in the development of CRS in dialysis patients.

C. Vida et al. have shown in dialysis patients the activation of peripheral blood polymorphonuclear and mononuclear leukocytes, which leads to excess production of oxidative compounds such as reactive oxygen species, and it is this process that plays the leading role [34].

The imbalance between the RAAS, sympathetic nervous system, and inflammation speeds up the CRS formation in dialysis patients. To prevent and slow the cardiac pathology in HD treatment, highly purified dialysis solutions and synthetic

dialysis membranes are being developed to reduce the risk of oxidative stress and other manifestations caused by low biocompatibility of membranes. For example, dialysis membranes made of regenerated cellulose that interact with the β-D-glucose hydroxyl groups of blood components cause activation of the complement system and leukopenia. To improve the biocompatibility of these membranes, hydroxyl groups are modified chemically by acetylation to produce triacetate cellulose or addition of D-α-tocopherol polyethylene glycol-1000 succinate chains, an esterified form of α-tocopherol. HD and PD in CKD permanently excrete antioxidants through the membranes. To normalize their blood levels and suppress ROS generation in patients on HD, vitamins C, E, and glutathione are supplemented orally [27].

3. Protein and energy deficiency and dialysis cachexia

PEM should be noted among the factors influencing the progression of cardiovascular pathology and the formation of CRS in patients on dialysis [35, 36]. Progressive blood pressure instability with LVH and diastolic dysfunction, acidosis, coronary atherosclerosis, as well as increasing hypoalbuminemia and severe anemia early lead to ineffective HD and loss of residual renal function. These exacerbate hyperhydration with overload and ischemia of myocardial muscle, oxidative stress, and heart chamber dilatation.

The causes of PEM in dialysis patients include protein hypercatabolism with decreased synthesis of albumin and essential amino acids and their subsequent losses (more on PD), L-carnitine deficiency, anorexia with depression, and chronic inflammation with hyperproduction of pro-inflammatory cytokines [37]. Uremic hyperparathyroidism with deficiency of anabolic hormones (insulin, erythropoietin) plays an important role in the PEM development. Progression of PEM is fixed by monitoring of anthropometry (BMI, shoulder muscle circumference, and triceps skinfold), levels of albumin, lymphocytes, TNF-α, transferrin, and CRP.

In the advanced stage of dialysis CRS, PEM progresses to MIA-syndrome (Malnutrtion, Inflammation, Atherosclerosis). This is manifested by ischemic cardiomyopathy provoking arrhythmias, stenotic atherosclerosis with diffuse calcification of arteries and heart valves, and treatment-resistant anemia and hypoalbuminemia [38].

Dialysis cachexia in MIA syndrome is formed in BMI under 15 kg/m^2 with hypoalbuminemia (<30 g/l). Clinically it manifests by severe cardiovascular, endocrine, and immune disorders [39]. It is characteristic of the late stage of CRS, when dialysis cachexia is aggravated by cachexia of chronic heart failure (CHF). The formed CHF aggravates PEM because of acidosis with additional hypercatabolism, oxidative stress, impaired absorption syndrome and hypoalbuminemia, and polypragmasia. These patients have poorly controlled hypertension with recurrent intra-dialysis hypotension, ischemic cardiomyopathy with arrhythmias, widespread coronary atherosclerosis and calcinosis, severe hyperparathyroidism, and encephalopathy. There is a high risk of dementia and infection with outcome in bacterial sepsis. Successful treatment of anorexia, hypoalbuminemia, infectious complications, and encephalopathy is possible only with a comprehensive correction of depression, immunodeficiency (anti-cytokines, antibiotics), anemia, amino acid and L-carnitine deficiency, tube (parenteral) feeding, and infusion of proteins. In severe cachexia, kidney transplantation is effective.

4. Influence of residual kidney function reduction on progression of cardiovascular pathology in patients on RRT

Preservation of residual kidney function in dialysis patients improves their survival and prognosis. For example, Dutch joint NECOSAD study [40] in 740 patients on HD showed an increase in residual kidney function (Kt/V by 1 unit) associated with a 66% reduction in the relative risk of death. Prospective analysis by W. Van der Wal et al., which included 1800 dialysis patients (1191 patients were on HD and 609 on PD), found a 1.5-fold death risk increase after loss of residual renal function compared to patients with preserved residual renal function [41]. Y. Obi et al. found that higher and more stable residual renal function (GFR) was associated with better patient survival one year after initiation of regular HD. Mortality related inversely with residual renal function measured by urea clearance and daily urine output [42]. In several other multicenter studies [43, 44] residual function has been an independent predictor of survival in patients on PD. The Canadian-American Study (CANUSA) [45] showed on 601 patients on PD that residual renal function rather than peritoneal creatinine clearance and peritoneal ultrafiltration (UF) correlate with patient survival. A study of residual renal function in PD patients showed a 36% reduction in the relative risk of death with an increase in daily urine output by 250 mL.

Preservation of residual renal function provides better control of hyperhydration, dyselectrolytemia, inflammatory activity, and clearance of protein-bound low molecular weight toxins and medium-molecular-weight molecules. Even a small amount of residual function reduces the level of plasma dissolved uremic toxins and β_2-microglobulin [46–48].

The residual renal function allows to reduce cardiac mortality and progression of cardiovascular disease in dialysis patients primarily through better hydration control. Both on regular and continuous PD, CKD patients with uncorrected hyperhydration are at high risk of developing cardiovascular complications: volume/sodium-dependent hypertension, left ventricular hypertrophy, arrhythmias, and congestive heart failure [49–51]. The expansion of intravascular volume leads to elongation of myocardial cells, and eccentric or asymmetrical left ventricular remodeling [52].

In patients on intermittent HD, UF causes post-ischemic impairment of myocardial contractile function (myocardial stunning) even in the absence of angiographically significant coronary disease [53]. Recurrent UF-induced ischemia provokes chronic left ventricular dysfunction, a cause of CHF progression in patients on HD [54]. Preserved residual renal function in patients on regular PD allows to reduce UF volumes during dialysis session, thus reducing risk of recurrent myocardial ischemia or systolic pressure drop during the session (hemodialysis-induced hypotension) [54–57]. In patients on PD, maintenance of residual renal function and significant diuresis attenuates the damaging effects of dextrose on the peritoneal membrane and reduces hyperglycemia and the risk of obesity and diabetes.

The residual renal function not only increases survival but also improves hormonal, mineral-bone, and nutritional disorders and the quality of life in patients on HD and PD, as confirmed by the CHOICE study [58]. Higher quality of life in patients with diuresis over 250 ml per day is also associated with a less restriction in diet and fluid intake, and better nutritional status [59] and control of hyperphosphatemia, renal osteodystrophy, and anemia. The latter depend on a renal synthesis of erythropoietin and active forms of vitamin D_3 in kidneys [60, 61]. Several data have shown an association between the preserved residual

renal function and decreased production of inflammatory markers: C-reactive protein and interleukin-6 [62, 63].

5. Ultrafiltration, hemodialysis-induced hypotension and metabolic acidosis

In patients with end stage CKD, fluid removal is achieved by extracorporeal UF with HD or intracorporeal UF with continuous PD. Unlike intermittent HD, continuous PD is not associated with "stunned" myocardium, which largely explains the slower progression of CHF in patients treated with PD [64]. However, clinical studies showed contradictory results on the benefits of PD. *V.* Panday et al. found in a retrospective analysis of 139 patients with CKD stage 5 and concomitant CHF no difference in two-year mortality, cardiac outcomes, and hospitalization rates between patients on PD and HD [65]. In a study using the Taiwan National Database with over 35,000 patients, I. Wang et al. showed lower survival of ESRD patients and comorbid CHF on the PD treatment [66]. However, the findings could be related to difficulties in hydration management on PD, complete loss of residual renal function, and/or shortcomings and limitations of the analysis performed. In a registry analysis in Lombardy, F. Locatelli et al. found no significant difference in the magnitude of cardiovascular risk in the groups treated with HD compared to that on PD [67]. Recent studies based on the Taiwan National Registry (2016), which included over 45,000 patients with end stage CKD, showed the 29% higher risk of cardiovascular disease in patients treated with HD compared to those treated with PD [68].

The development of intradialysis hypotension on regular HD is caused by uremic polyneuropathy and CHF, when, in response to dialysis UF, the vascular bed fills inadequately slowly, causing hypovolemia and hypotension. Dialysis CRS with hypotension is often complicated by thrombosis of vascular access, resulting in rapid formation of underdialysis syndrome with hypercatabolism. Blood loss and sinus tachycardia combined with hemodialysis-induced hypotension significantly increase the risk of acute coronary syndrome and cerebrovascular accident (CVA). Patients with diabetic nephropathy often develop severe hemodialysis-induced hypotension refractory to conservative therapy. The hypotension can provoke target organ ischemia. Vasopressors and alpha-adrenergic agonists are not safe in treating hemodialysis-induced hypotension. Controlled UF with "dry weight" monitoring by bio-impedance, transfer to PD, or daily (nighttime) HD are recommended.

Metabolic acidosis is common in patientswith ESRD because of a decreased ability to excrete acids and reduced renal synthesis of bicarbonate. It leads to malnutrition, inflammation, bone disease disorders, and even a higher death risk [69]. Significant acid–base variations during dialysis may play an important role in CVD development in HD patients. One study [70] has shown an association between low serum bicarbonate concentrations and cardiovascular disease in patients on dialysis. It is important to avoid large variations in serum bicarbonate levels in dialysis patients because these variations can increase CVD.

6. Stenotic atherosclerosis

MIA syndrome is characterized by rapid stenosing of the major arteries by the progressing atherosclerosis combined with calcinosis. Frequent complications are ischemic kidney disease with uncontrolled renin-dependent hypertension, stenotic

atherosclerosis of cerebral arteries with the risk of CVA, ischemic occlusive enteropathy with malabsorption syndrome aggravating PEM and anemia.

In dialysis CRS with the expanded PEM, coronary heart disease (CHD) is typical with unstable angina and elevated blood CRP correlating with LDL levels [71, 72]. Hyperparathyroidism is associated with progressive coronary artery calcification, increasing atherosclerosis [73, 74]. Stenosis of the proximal coronary artery is typical, which causes high mortality in patients on dialysis [75]. Early diagnosis of myocardial infarction in dialysis CRS is difficult because of confounding uremic polyneuropathy, dyselectrolitemia, myocardial calcification, and coronary calcinosis. Coronarography in 60% of patients with CKD stage 5 admitted for regular HD treatment in Japan reveals low-symptomatic stenosis of one coronary artery and of several coronary arteries (multivessel disease) in some patients.

To prevent acute coronary syndrome, risk factors should be addressed in HD: hemodialysis-induced hypotension, sinus tachycardia, blood loss, and anemia. ACE inhibitors reduce the cardiac mortality [76]. Nitrates and beta-blockers are tolerated worse in dialysis CRS because of hemodynamic instability.

Hemodialysis-induced myocardial ischemiamight regress with the use of beta-blockers, which have substantially improved survival in patients with acute coronary syndromes and heart failure. In dialysis patients, carvedilol significantly improved cardiovascular mortality, LV function, and LV morphology. Dialysis patients treated with carvedilol had a 50% lower mortality rate than patients receiving placebo [77, 78]. The efficacy of statins on regular HD has not been proven conclusively, and the incidence of side effects is higher than in the early stages of CKD [79].

Current guidelines by KDIGO recommend not starting lipid-lowering therapy in dialysis patients. These recommendations are based on clinical trials which failed to show that statin therapy is beneficial in reducing cardiovascular mortality indialysis patients, in contrast to the general population [80]. High-density lipoprotein cholesterol (HDL-C) from HD patients compared to healthy controls has been much less effective in cholesterol efflux and regulation of inflammation [81]. HDL-C from HD patients promotes endothelial dysfunction via accumulation of symmetric dimethylarginine (SDMA), which is associated with increased all-cause and cardiovascular mortality [82].

Erythropoietin drugs cannot fully realize their cardioprotective effect because of more frequent side effects of the high doses. Survival rate after acute myocardial infarction is extremely low at conservative therapy of CHD on hemodialysis (by the end of the 1st year, 41%, after 2 years, 27%, after 3 years, 10%). This causes intolerance of uremic myocardium to ischemia with small coronary artery remodeling (uremic small vessel disease) and myocardial stunning on HD. In coronary angioplasty in patients with dialysis-related CRS, the acute postoperative mortality is over 3.5 times higher than the statistical average, and the long-term survival rate after stenting is significantly higher than in conservative therapy [83].

7. Progressive CHF with low cardiac output

CHF in patients on HD is manifested by worsening chronic hypervolemia, causing both circuits decompensation and a significant decrease in ejection fraction preventing effective HD, and development of critical progressive hyponatremia with a high risk of cerebral edema. The 3-year survival rate of patients with CHF on regular HD does not exceed 20%, and sudden cardiac death is most frequent fatality in this group of patients on HD [84].

The rate of sudden cardiac death is 59 deaths in 1000 patient-years in the CKD stage 5D population, whereas it is 1 death in 1000 patient-years in the general population [85]. Patients on dialysis have a high incidence of coronary heart disease, but the rate of sudden cardiac death is disproportionately high compared with the incidence of coronary heart disease in these patients. Even a complete revascularization reduce the risk of sudden cardiac death only in part [86]. Dialysis, especially HD, is a risk factor for sudden cardiac death, providing the highest risk within the first 12 hours after dialysis and after a long dialysis-free interval [87]. Potential mechanisms include volume and sudden electrolyte shifts after dialysis, volume overload, and electrolyte disturbance.

These outcomes largely depend not on the severity of CHD, but on the value of the corrected QT-interval and QT dispersion and are caused by complex rhythm disturbances in dialysis malnutrition (hypercatabolism, acidosis, imbalance of potassium, sodium and calcium in dialysis solution, and hypomagnesemia) [88]. Cardioprotectors, antiarrhythmics, and vasopressors provide only short-term effect; myocardial reperfusion, artificial pacemaker, implanted cardioverter-defibrillator are more effective [84, 88].

PD may be the method of choice in the treatment of patients with CHF, providing effective UF and sodium excretion in the required volumes, especially when using icodextrin solution. In patients with CRS and severe ascites, PD can reduce intra-abdominal pressure. PD in patients with CHF has several advantages: continuous "mild" UF with minimal impact on hemodynamics and reduction of volume overload symptoms; weight reduction and correction of hypervolemia; increase in left ventricular ejection fraction; sodium "sieving" effect and better control of hypernatremia; removal of acute phase proteins, medium-molecular-weight molecules, abscence of pro-inflammatory activation of cytokines; reduction of intraabdominal pressure and improved quality of life in patients with severe ascites; and better control of serum potassium level with the possibility of using aldosterone receptor blockers and ACE inhibitors. Heart transplantation should be used in refractory cases, sometimes in combination with the kidney transplantation.

8. Vascular calcification

Hyperparathyroidism, frequent in RRT patients, is prognostically unfavorable [89]. Elevation of serum fibroblast growth factor-23 (FGF-23) with the development of resistance to it precedes Mineral Bone Disease (MBD). Elevated FGF23 levels were independently associated with LVH.FGF23 caused LVH via FGF receptor-dependent activation of the calcineurin-nuclear factor of activated T-cells signaling pathway [90]. Klotho deficiency and FGF23 elevation are associated with poor outcomes and complications in dialysispatients. Klotho deficiency cause vascular calcification, cardiac fibrosis, and cardiac hypertrophy in patients with CKD [91].

Hyperphosphatemia and parathyroid hormone elevation increase with increasing stage of CKD and correlate with cardiac mortality [92]. This is largely because of vascular calcification, especially pronounced in dialysis patients, which is associated with the use of solutions for PD and HD with increased calcium content.

Vascular calcification (VC) is defined as vascular deposition of calcium-phosphate mineral complexes. Traditionally, two forms of calcification are pointed out: 1) intimal calcification in proximity to lipid deposits, clinically relevant in obstructive arterial disease and 2) medial calcification with differentiation of smooth muscle cells into osteoblast-like cells is akin to bone formation, related to several genes as BMP2, Msh Homeobox 2, and gene of alkaline phosphatase [93].

Medial calcification is common in dialysis patients with CKD.VC has a clearrelationship with atherosclerotic vascular disease [94]. Calcification of arterial vessels leads to arterial stiffness, contributes to increased pulse wave velocity, increased cardiac afterload, and thus heart failure [95]. Arterial stiffness is an independent predictor of cardiovascular mortality [96]. Arterial stiffness and medial calcification intensify each other, to create a vicious cycle [97]. Heart valve calcification occurs in stage 5 CKD in up to 88–99% of patients, increasing from 40% of patients in CKD stage 3 [98].

Calcinosis of heart valves leads to the formation of acquired heart valvular disease (aggravating CHF) and increases the risk of infective endocarditis. The extent of vascular calcifications in CKD herald a poor prognosis [99]. Resulting hemodynamic alterations induce left ventricular hypertrophy associated with a decrease in coronary perfusion [100].

In dialysis CRS, active vitamin D metabolites are contraindicated because of the risk of soft tissue calcification (including skin calcification with sepsis). Calcium-free phosphate binders are advisable: sevelamer, lanthanum carbonate [101]. Sevelamer corrects hyperphosphatemia and decreases mortality in dialysis patients by 1.5 times, slowing coronary calcification, reducing blood levels of atherogenic lipids, FGF-23, and pro-inflammatory cytokines [102]. Iron-containing phosphate binders effectively lower blood phosphate levels, but are often complicated by diarrhea and nutritional disorders exacerbation in PEM [103]. Total parathyroidectomy in patients with dialysis cachexia is effective in MBD and CHF progression but carries a risk of acute postoperative complications [104]. An alternative to parathyroidectomy is administration of calcimimetics. Prolonged-release cinalcet reduces the need for parathyroidectomy, slows arterial and cardiac valve calcification, and reduces cardiovascular mortality [105, 106].

9. Immunodeficiency

In dialysis-associated CRS, infection is severe, both induced by thrombosis of sclerosed AVF or not associated with vascular access. Pneumonia risk factors in dialysis CRS with malnutrition include immune deficiency with activation of opportunistic infections and Staphylococcus carrying in the nasopharynx, CHF with chronic hyperhydration and hypoxia of lung tissue, hydrothorax, hyperparathyroidism with lung tissue calcification, obstructive night apnea syndrome, and epoetin-resistant anemia.

Pathogens of acute pneumonia on dialysis include staphylococcus, opportunistic bacteria (*E. Coli*, Haemophylis influenzae, Klebsiella, Pseudomonas, Listeria, Legionella), and pathogenic fungi (Aspergillus, Candida, Cryptococcus, Mucormyces). In dialysis CRS, the mortality is extremely high from pneumonia caused by the association of influenza virus with *Staphylococcus aureus* [107] or superinfection with pneumocysts in MIA syndrome patients infected with cytomegalovirus. At the advanced stage of CRS in diabetic patients, purulent complications of obliterating atherosclerosis of lower limb arteries and diabetic foot typically cause high mortality from gangrene and sepsis. Risk factors for infectious endocarditis in dialysis CRS are vascular access infection, calcinosis of valves in severe hyperparathyroidism, their myxomatous degeneration, thrombotic deposits, or severe anemia [108].

Antibiotic therapy is carried out after removal of the infected fistula with the formation of a new AVF or with transfer to PD [109]. Treatment with broad-spectrum antibiotics should be started immediately and corrected by the blood culture results. Antibiotic therapy is ineffective in CHF, recurrent

thromboembolism, fungal endocarditis, tricuspid or pulmonary artery valves lesions (frequent in HD patients). In these cases, surgery is necessary to replace the affected valve [108].

10. Epoetin-resistant anemia

Anemia in CKD patients induces eccentric LVH and exacerbates myocardial ischemia, increasing cardiovascular mortality in dialysis CRS [110, 111]. Erythropoietin drugs improve the quality of life of dialysis patients. However, the mortality-reducing effect of erythropoietin in dialysis CRS has not been proven, and the most effective and safe target Hb level is not established. The currently recommended target Hb level of 10–12 g/dL does not stimulate sufficiently neoangiogenesis and endothelial stem cells activity.

Resistant anemia often develops within MIA syndrome (under the influence of chronic inflammation, acidosis, iron malabsorption, vit. B12 and folic acid deficiency), as well as because of ineffective HD syndrome and hyperparathyroidism, requiring the unusually high doses of erythropoietin. Since this therapy is often complicated by poorly controlled hypertension and thrombosis, combined antihypertensive therapy, complete correction of iron deficiency, vit. B12 and metabolic acidosis, and control of the coagulation system are indicated [112]. Intensification of HD regimen, correction of hyperparathyroidism, influence on chronic inflammation syndrome (anti-cytokine drugs, etc.) are of great importance for overcoming resistance to epoetin. At critically low hemoglobin, blood transfusions can be used.

Recently, a new group of drugs has been proposed to treat anemia, the so called hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs). HIF-PHIs promote erythropoiesis primarily through increased endogenous EPO production and modulation of iron metabolism. The results of phase 2 and 3 clinical trials have shown their advantages, such as decreased hepcidin levels, better iron utilization and thus less need for iron, the ability to influence the background of inflammation without increasing the dose [113]. These drugs will probably find their use in patients with epoetin-resistant anemia associated with both inflammation and iron metabolism disorders.

11. Impact of arterio-venous hemodialysis fistula

In dialysis patients, one can assume the relationship between CHF and recent AVF formation in slight reduction of cardiac output, absence of pulmonary hypertension and other causes of heart failure progression (severe CHD, cardiomyopathy).

After AVF formation, peripheral vascular resistance decreases rapidly, leading to compensatory increase of cardiac output and possibly to acute CHF decompensation. Because of the increase of blood inflow to the heart, the diastolic size of the left ventricleand pulmonary pressure increase [114]. Subsequently, progressing myocardial hypertrophy and dilatation of heart cavities cause diastolic LV dysfunction and CHF development [115]. Pulmonary hypertension, found in 40–50% of patients on HD [116], joins soon after AVF formation and is associated with the size of arterio-venous shunt [117]. The inadequate pulmonary vasodilation in response to the AVF-induced increase in blood flow rate is thought to be caused by decreased NO synthesis in the endothelium or accumulation of uremic NO inhibitors, such as asymmetric dimethyl arginine [118].

In all patients on regular HD, AVF with a large shunt should be considered as a factor aggravating the CHD and CHF development. Normalization of blood flow in AVF can lead to delay in cardiovascular pathology progression. In peripheral bypass syndrome, blood flow and perfusion in the limb distal to the fistula reduce dramatically because of shunt redistribution of blood flow. Less known is coronary bypass syndrome, where left-sided AVF, bypassing the left internal thoracic artery, reduces coronary blood flow, which can lead to myocardial ischemia, especially during the HD session [119].

After the AVF formation, the blood volume increases to maintain a higher cardiac output and can be complicated by severe (refractory) hypertension. In several "preload (end-diastolic pressure)-dependent" dialysis patients, poorly controlled dialysis-induced hypotension accompanies inter-dialysis hypertension in the first 15–20 min of HD even with moderate volumes of UF. Among other complications, fistula infection with outcome in progressing CHF and thromboembolic syndrome provokes prognostically unfavorable bacterial endocarditis.

Thus, AVF, being essentially an iatrogenic vascular anomaly formed to treat HD, can contribute to cardiac mortality. The negative effect of AVF on cardiovascular mortality is directly proportional to blood flow in the fistula and severity of initial cardiovascular pathology. Thus, AVF should not be used in patients with LV ejection fraction <40% and significant pulmonary hypertension. Therefore, the AVF formation should be preceded by cardiac assessment (ECG and Echo-CG monitoring) involving a consultation with a cardiologist.

AVF formation should be planned 2–3 months before the expected start of HD. It is unwise to form AVF a year or more before the start of HD and at Hb levels >12 g/dL because of high risk of fistula thrombosis. Blood flow in the fistula should be targeted at 400–600 ml/min; for blood flow over 800 ml/min, surgical reduction of arterio-venous blood shunt is reasonable. Ultrasonography, venography, and arteriography (fistulography) are used to monitor AVF.

In patients with refractory CHF, CHD with unstable angina, coronary or peripheral bypass syndrome, or severe pulmonary hypertension, AVF ligation with transfer to CAPD is indicated. In endocarditis after removal of infected AVF is recommended temporary transfer of a patient with HD to CAPD or low-flow dialysis, increasing the effectiveness of antibiotic therapy, followed by prosthetic heart valves insertion. PD can be used also for the period of standard AVF formation and maturation instead of AVF with excessive shunt.

12. Conclusion

Further study is important of cardiorenal relationships in patients on RRT with the isolation of a separate "dialysis-related" type of CRS reflecting the progression of cardiac dysfunction during dialysis treatment. To analyze the features of dialysis CRS, a comprehensive approach should be developed for its treatment and prevention.

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References

[1] Ronco C, McCullough P, Anker SD, et al. Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. Eur Heart J. 2010; 31(6):703-711. doi:10.1093/ eurheartj/ ehp507

[2] Vanholder R, Massy Z, Argiles A, et al. Chronic kidney disease as a cause of cardiovascular morbidity and mortality. Nephrol Dial Transplant. 2005; 20(6):1048-1056. doi:10.1093/ ndt/gfh813

[3] Zoccalli C. Cardiorenal risk as a new frontier of nephrology: research needs and areas for intervention. Nephrol Dial Transplant. 2002; 17 Suppl 11:50-54. doi:10.1093/ndt/17.suppl_11.50

[4] London G, Marchais S, Guerin A, et al. Inflammation, arteriosclerosis, and cardiovascular therapy in hemodialysis patients. Kidney Int Suppl. 2003; 84:S88-S93. doi:10.1046/j. 1523-1755.63.s84.25.x

[5] Libetta C, Sepe V, Esposito P, Galli F, Dal Canton A. Oxidative stress and inflammation: implications in uremia and hemodialysis. Clin Biochem. 2011; 44(14-15):1189-1198. doi:10.1016/j. clinbiochem.2011.06.988

[6] Mares J, Richtrova P, Hricinova A, et al. Proteomic profiling of blood-dialyzer interactome reveals involvement of lectin complement pathway in hemodialysis-induced inflammatory response. Proteomics Clin Appl. 2010; 4(10-11):829-838. doi:10.1002/prca.201000031

[7] Brunini T, Mendes-Ribeiro A, Ellory J, Mann G. Platelet nitric oxide synthesis in uremia and malnutrition: a role for L-arginine supplementation in vascular protection? Cardiovasc Res. 2007; 73(2):359-367. doi:10.1016/j. cardiores.2006.09.019

[8] Locatelli F, Del Vecchio L, Pozzoni P, Andrulli S. Dialysis adequacy and response to erythropoiesis-stimulating agents: what is the evidence base? Semin Nephrol. 2006; 26(4):269-274. doi:10.1016/j.semnephrol.2006.05.002

[9] Elliott J, Mishler D, Agarwal R. Hyporesponsiveness to erythropoietin: causes and management. Adv Chronic Kidney Dis. 2009; 16(2):94-100. doi:10.1053/j.ackd.2008.12.004

[10] Van der Steen A. Research on dialyzers with improved biocompatibility. Clin Nephrol. 1986; 26 Suppl 1:S39-S42. PMID:3829466

[11] Rousseau Y, Carreno MP, Poignet JL, Kazatchkine MD, Haeffner-Cavaillon N. Dissociation between complement activation, integrin expression and neutropenia during hemodialysis. Biomaterials. 1999; 20(20):1959-1967. doi:10.1016/s0142-9612(99)00101-5

[12] Del Vecchio L, Locatelli F, Carini M. What we know about oxidative stress in patients with chronic kidney disease on dialysis – clinical effects, potential treatment, and prevention. Semin Dial. 2011; 24(1):56-64. doi:10.1111/j. 1525-139X.2010.00819.x

[13] Jansen M, Hart A, Korevaar J, et al; NECOSAD Study Group. Predictors of the rate of decline of residual renal function in incident dialysis patients. Kidney Int. 2002; 62(3):1046-1053. doi:10.1046/j.1523-1755.2002.00505.x

[14] 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. doi:10.1155/ 2017/3494867

[15] Roumeliotis S, Eleftheriadis T, Liakopoulos V. Is oxidative stress an

issue in peritoneal dialysis? Semin Dial. 2019; 32(5):463-466. doi:10.1111/sdi.12818

[16] Krata N, Zagożdżon R, Foroncewicz B, Mucha K. Oxidative stress in kidney diseases: the cause or the consequence? Arch Immunol Ther Exp (Warsz). 2018; 66(3):211-220. doi:10.1007/s00005-017-0496-0

[17] Ikizler T, Morrow J, Roberts L, et al. Plasma F2-isoprostane levels are elevated in chronic hemodialysis patients. Clin Nephrol. 2002; 58(3):190-197. doi:10.5414/cnp58190

[18] Ferraro B, Galli F, Frei B, et al. Peroxynitrite-induced oxidation of plasma lipids is enhanced in stable hemodialysis patients. Kidney Int. 2003; 63(6):2207-2213. doi:10.1046/j.1523-1755.2003.00008.x

[19] Muller C, Eisenbrand G, Gradinger M, et al. Effects of hemodialysis, dialyser type and iron infusion on oxidative stress in uremic patients. Free Radic Res. 2004; 38(10):1093-1100. doi:10.1080/10715760400011452

[20] Galli F, Benedetti S, Floridi A, Canestrari F, Piroddi M. Glycoxidation and inflammatory markers in patients on treatment with PMMA-based protein-leaking dialyzers. Kidney Int. 2005; 67(2):750-759. doi:10.1111/j.1523-1755.2005.67138.x

[21] Piroddi M, Palmese A, Pilolli F, et al. Plasma nitroproteome of kidney disease patients. Amino Acids. 2011; 40(2):653-667. doi:10.1007/s00726-010-0693-1

[22] Thornalley P, Rabbani N. Protein damage in diabetes and uremia – identifying hotspots of proteome damage where minimal modification is amplified to marked pathophysiological effect. Free Radic Res. 2011; 45(1):89-100. doi:10.3109/10715762.2010.534162

[23] Vanholder R, Baurmeister U, Brunet P, et al. A bench to bedside view of uremic toxins. J Am Soc Nephrol. 2008; 19(5):863-870. doi:10.1681/ASN.2007121377

[24] Vanholder R, Schepers E, Meert N, Lameire N. What is uremia? Retention versus oxidation. Blood Purif. 2006; 24(1):33-38. doi:10.1159/000089434

[25] De Smet R, Dhondt A, Eloot S, et al. Effect of the super-flux cellulose triacetate dialyser membrane on the removal of non-protein-bound and protein-bound uraemic solutes. Nephrol Dial Transplant. 2007; 22(7):2006-2012. doi:10.1093/ndt/gfm065

[26] Thomas G, Jaber B. Convective therapies for removal of middle molecular weight uremic toxins in end-stage renal disease: a review of the evidence. Semin Dial. 2009; 22(6):610-614. doi:10.1111/j.1525-139X.2009.00665.x

[27] Galli F, Piroddi M, Annetti C, et al. Oxidative stress and reactive oxygen species. Contrib Nephrol. 2005; 149:240-260. doi:10.1159/000085686

[28] Sanchez-Lozada LG, Tapia E, Johnson RJ, Rodríguez-Iturbe B, Herrera-Acosta J. Glomerular hemodynamic changes associated with arteriolar lesions and tubulointerstitial inflammation. Kidney Int Suppl. 2003; 86:S9-14. doi:10.1046/j.1523-1755.64.s86.3.x

[29] Niijima A, Hori T, Aou S, Oomura Y. The effects of interleukin-1β on the activity of adrenal, splenic and renal sympathetic nerves in the rat. J Auton Nerv Syst. 1991; 36(3):183-192. doi:10.1016/0165-1838(91)90042-2

[30] Wassmann S, Stumpf M, Strehlow K, et al. Interleukin-6 induces oxidative stress and endothelial dysfunction by overexpression of the angiotensin II type 1 receptor. Circ Res.

2004; 94(4):534-541. doi:10.1161/01.RES.0000115557.25127.8D

[31] Tsutamoto T, Hisanaga T, Wada A, et al. Interleukin-6 spillover in the peripheral circulation increases with the severity of heart failure, and the high plasma level of interleukin-6 is an important prognostic predictor in patients with congestive heart failure. J Am Coll Cardiol. 1998; 31(2):391-398. doi:10.1016/s0735-1097(97)00494-4

[32] Anker SD, Egerer KR, Volk HD, et al. Elevated soluble CD14 receptors and altered cytokines in chronic heart failure. Am J Cardiol. 1997; 79:1426-1430. doi:10.1016/s0002-9149(97)00159-8

[33] Kawai M, Naruse K, Komatsu S, et al. Mechanical stress-dependent secretion of interleukin 6 by endothelial cells after portal vein embolization: clinical and experimental studies. J Hepatol. 2002; 37(2):240-246. doi:10.1016/s0168-8278(02)00171-x

[34] Vida C, Oliva C, Yuste C, et al. Oxidative stress in patients with advanced ckd and renal replacement therapy: the key role of peripheral blood leukocytes. Antioxidants (Basel). 2021; 10(7):1155. doi:10.3390/antiox10071155

[35] Gama-Axelsson T, Heimburger D, Stevinkel P, et al. Serum albumin as predictor of nutritional status in patients with ESRD. Clin J Am Soc Nephrol. 2012; 7(9):1446-1453. doi:10.2215/CJN.10251011

[36] Carrero JJ, Avesani CM. Pros and cons of body mass index as a nutritional and risk assessment tool in dialysis patients. Semin Dial. 2015; 28(1): 48-58. doi:10.1111/sdi.12287

[37] Kovesdy CP. Malnutrition in dialysis patients - the need for intervention despite uncertain benefits. Semin Dial. 2016; 29(1):28-34. doi:10.1111/sdi.12410

[38] Kalantar-Zadeh K, Ikizler TA, Block G, Avram MM, Kopple JD. Malnutrition-Inflammation complex syndrome in dialysis patients: causes and consequences. Am J Kidney Dis. 2003; 42(5):864-881. doi:10.1016/j.ajkd.2003.07.016

[39] De Roij van Zuijdewijn CL, ter Wee PM, Chapdelaine I, et al. A comparison of 8 nutrition-related tests to predict mortality in haemodialysis patients. J Ren Nutr. 2015; 25(5):412-419. doi:10.1053/j.jrn.2015.02.005

[40] Termorshuizen F, Dekker FW, van Manen JG, et al; NECOSAD Study Group. Relative contribution of residual renal function and different measures of adequacy to survival in hemodialysis patients: an analysis of the Netherlands cooperative study on the adequacy of dialysis (NECOSAD)-2. J Am Soc Nephrol. 2004; 15(4):1061-1070. doi:10.1097/01.asn.0000117976.29592.93

[41] van der Wal WM, Noordzij M, Dekker FW, et al. Full loss of residual renal function causes higher mortality in dialysis patients; findings from a marginal structural model. Nephrol Dial Transplant. 2011; 26(9):2978-2983. doi:10.1093/ndt/gfq856

[42] Obi Y, Streja E, Rhee C, et al. Incremental hemodialysis, residual kidney function, and mortality risk in incident dialysis patients: a cohort study. Am J Kidney Dis. 2016; 68(2):256-265. doi:10.1053/j.ajkd.2016.01.008

[43] Diaz-Buxo JA, Lowrie EG, Lew NL, et al. Associates of mortality among peritoneal dialysis patients with special reference to peritoneal transport rates and solute clearance. Am J Kidney Dis. 1999; 33(3):523-534. doi:10.1016/s0272-6386(99)70190-3

[44] Rocco M, Soucie JM, Pastan S, McClellan WM. Peritoneal dialysis adequacy and risk of death. Kidney Int.

2000; 58(1):446-457. doi:10.1046/j.1523-1755.2000.00184.x

[45] Bargman JM, Thorpe KE, Churchill DN. Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. J Am Soc Nephrol. 2001; 12(10):2158-2162. doi:10.1681/ASN.V12102158

[46] Kabanda A, Jadoul M, Pochet JM, et al. Determinants of the serum concentrations of low molecular weight proteins in patients on maintenance hemodialysis. Kidney Int. 1994; 45(6):1689-1696. doi:10.1038/ki.1994.221

[47] Stompór T., Sułowicz W., Anyszek T. et al. Dialysis adequacy, residual renal function and serum concentrations of selected low molecular weight proteins in patients undergoing continuous ambulatory peritoneal dialysis. Med Sci Monit. 2003; 9(11):CR500-CR504. PMID:14586277

[48] Delaney MP, Stevens PE, Al Hasani M, et al. Relationship of serum cystatin C to peritoneal and renal clearance measures in peritoneal dialysis: a cross-sectional study. Am J Kidney Dis. 2008; 51(2):278-284. doi:10.1053/j.ajkd.2007.08.018

[49] Gunal AI, Kirciman E, Guler M, Yavuzkir M, Celiker H. Should the preservation of residual renal function cost volume overload and its consequence left ventricular hypertrophy in new hemodialysis patients? Ren Fail. 2004; 26(4):405-409. doi:10.1081/jdi-120039825

[50] Voroneanu L, Cusai C, Hogas S, et al. The relationship between chronic volume overload and elevated blood pressure in hemodialysis patients: use of bioimpedance provides a different perspective from echocardiography and biomarker methodologies. Int Urol Nephrol. 2010; 42(3):789-797. doi:10.1007/s11255-010-9767-y

[51] Hassan K, Hassan S, Anwar S, et al. Predictors of left ventricular hypertrophy and their cutoffs in peritoneal dialysis patients. Int Heart J. 2015; 56(2):186-191. doi:10.1536/ihj.14-246

[52] Di Lullo L, Gorini A, Russo D, Santoboni A, Ronco C. Left ventricular hypertrophy in chronic kidney disease patients: from pathophysiology to treatment. Cardiorenal Med. 2015; 5(4):254-266. doi:10.1159/000435838

[53] McIntyre CW, Burton JO, Selby NM, et al. Hemodialysis-induced cardiac dysfunction is associated with an acute reduction in global and segmental myocardial blood flow. Clin J Am Soc Nephrol. 2008; 3(1):19-26. doi:10.2215/CJN.03170707

[54] Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. Clin J Am Soc Nephrol. 2009; 4(12):1925-1931. doi:10.2215/CJN.04470709

[55] Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. Clin J Am Soc Nephrol. 2009; 4(5): 914-920. doi:10.2215/CJN.03900808

[56] Dorairajan S, Chockalingam A, Misra M. Myocardial stunning in hemodialysis: what is the overall message? Hemodial Int. 2010; 14(4):447-450. doi:10.1111/j.1542-4758.2010.00495.x

[57] McIntyre CW. Haemodialysis-induced myocardial stunning in chronic kidney disease – a new aspect of cardiovascular disease. Blood Purif. 2010; 29(2):105-110. doi:10.1159/000245634

[58] Shafi T, Jaar BG, Plantinga LC, et al. Association of residual urine output with mortality, quality of life, and inflammation in incident hemodialysis patients: the choices for healthy outcomes in caring for end-stage renal disease (CHOICE) study. Am J Kidney Dis. 2010; 56(2):348-358. doi:10.1053/j.ajkd.2010.03.020

[59] Suda T, Hiroshige K, Ohta T, et al. The contribution of residual renal function to overall nutritional status in chronic haemodialysis patients. Nephrol Dial Transplant. 2000; 15(3):396-401. doi:10.1093/ndt/15.3.396

[60] Vilar E, Wellsted D, Chandna SM, Greenwood RN, Farrington K. Residual renal function improves outcome in incremental haemodialysis despite reduced dialysis dose. Nephrol Dial Transplant. 2009; 24(8):2502-2510. doi:10.1093/ndt/gfp071

[61] Penne EL, van der Weerd NC, Grooteman MP, et al. Role of residual renal function in phosphate control and anemia management in chronic hemodialysis patients. Clin J Am Soc Nephrol. 2011; 6(2):281-289. doi:10.2215/CJN.04480510

[62] Wang AY, Wang M, Woo J, et al. Inflammation, residual kidney function, and cardiac hypertrophy are interrelated and combine adversely to enhance mortality and cardiovascular death risk of peritoneal dialysis patients. J. Am. Soc. Nephrol. 2004; 15(8):2186-2194. doi:10.1097/01.ASN.0000135053.98172.D6

[63] Palomo-Piñón S, Mora-Villalpando CJ, Del Carmen Prado-Uribe M, et al. Inflammation and myocardial damage markers influence loss of residual renal function in peritoneal dialysis patients. Arch Med Res. 2014; 45(6):484-488. doi:10.1016/j.arcmed.2014.07.003

[64] Selby NM, McIntyre CW. Peritoneal dialysis is not associated with myocardial stunning. Perit Dial Int. 2011; 31(1):27-33. PMID:20522673

[65] Panday VB, Tong ZP, Ng PL, et al. Dialysis modality and 2-year outcomes in patients with ischemic cardiomyopathy and end-stage renal disease. Int J Cardiol. 2014; 176(3):1097-1099. doi:10.1016/j.ijcard.2014.07.120

[66] Wang IK, Kung PT, Kuo WY, et al. Impact of dialysis modality on the survival of end-stage renal disease patients with or without cardiovascular disease. J Nephrol. 2013; 26(2):331-341. doi:10.5301/jn.5000149

[67] Locatelli F, Marcelli D, Conte F, et al. Survival and development of cardiovascular disease by modality of treatment in patients with end-stage renal disease. J Am Soc Nephrol. 2001; 12(11):2411-2417. doi:10.1681/ASN.V12112411

[68] Wang IK, Lu CY, Lin CL, et al. Comparison of the risk of de novo cardiovascular disease between hemodialysis and peritoneal dialysis patients with end-stage renal disease. Int J Cardiol. 2016; 218:219-224. doi:10.1016/j.ijcard.2016.05.036

[69] Vashistha T, Kalantar-Zadeh K, Molnar MZ, Torlén K, Mehrotra R. Dialysis modality and correction of uremic metabolic acidosis: relationship with all-cause and cause-specific mortality. Clin J Am Soc Nephrol. 2013; 8(2):254-264. doi:10.2215/CJN.05780612

[70] Raikou VD, Kyriaki D. Association between low serum bicarbonate concentrations and cardiovascular disease in patients in the end-stage of renal disease. Diseases. 2016; 4(4):36. doi:10.3390/diseases4040036

[71] Stenvinkel P. C-reactive protein: does it promote vascular disease? Nephrol Dial Transplant. 2006; 21(10):2718-2720. doi:10.1093/ndt/gfl317

[72] Amann K, Ritz C, Adamczak M, Ritz E. Why is coronary heart disease of uraemic patients so frequent and so devastating? Nephrol Dial Transplant. 2003; 18(4):631-640. doi:10.1093/ndt/gfg059

[73] Goodman W, Goldin J, Kuizon BD, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med. 2000; 342(20):1478-1483. doi:10.1056/NEJM200005183422003

[74] Barreto DV, Barreto FC, Carvalho AB, et al. Coronary calcification in hemodialysispatients: the contribution of traditional and uremia-related risk factors. Kidney Int. 2005; 67(4):1576-1582. doi:10.1111/j.1523-1755.2005.00239.x

[75] Charytan D, Kuntz RE, Mauri L, DeFilippi C. Distribution of coronary artery disease and relation to mortality in asymptomatic hemodialysis patients. Am J Kidney Dis. 2007; 49(3):409-416. doi:10.1053/j.ajkd.2006.11.042

[76] McCullough PA, Sandberg KP, Yee J, Hudson MP. Mortality benefit of angionensin-converting enzyme inhibitors after cardiac events in patients with end-stage renal disease. J Renin Angiotensin Aldosterone Syst. 2002; 3(3):188-191. doi:10.3317/jraas.2002.040

[77] Cice G, Ferrara L, Di Benedetto A, et al. Dilated cardiomyopathy in dialysis patients--beneficial effects of carvedilol: a double-blind, placebo-controlled trial. J Am Coll Cardiol. 2001; 37(2):407-411. doi:10.1016/s0735-1097(00)01158-x.

[78] Cice G, Ferrara L, D'Andrea A, et al. Carvedilol increases two-year survivalin dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. J Am Coll Cardiol. 2003; 41(9):1438-1444. doi:10.1016/s0735-1097(03)00241-9.

[79] Baber U, Toto RD, de Lemos JA. Statins and cardiovascular risk reduction in patients with chronic kidney disease and end-stage renal disease. Am Heart Dis. 2007; 153(4):471-477. doi:10.1016/j.ahj.2006.10.042

[80] Wanner C, Tonelli M; Kidney Disease: improving global outcomes lipid guideline development work group members. KDIGO clinical practice guideline for lipid management in CKD: summary of recommendation statements and clinical approach to the patient. Kidney Int. 2014; 85(6):1303-1309. doi:10.1038/ki.2014.31.

[81] Yamamoto S, Yancey PG, Ikizler TA, et al. Dysfunctional high-density lipoprotein in patients on chronic hemodialysis. J Am Coll Cardiol. 2012; 60(23):2372-2379. doi:10.1016/j.jacc.2012.09.013.

[82] Zewinger S, Kleber ME, Rohrer L, et al. Symmetric dimethylarginine, high-density lipoproteins and cardiovascular disease. Eur Heart J. 2017; 38(20):1597-1607. doi:10.1093/eurheartj/ehx118.

[83] Liu JY, Birkmeyer NJ, Sanders JH, et al. Risks of morbidity and mortality in dialysis patients undergoing coronary artery bypass surgery. Circulation. 2000; 102(24):2973-2977. doi:10.1161/01.cir.102.24.2973

[84] US Renal Data System USRDS 2009 Annual Data Report: atlas of chronic kidney disease and end-stage renal disease in the United States, National Institutes of health, National Institute of diabetes and digestive and kidney diseases. Bethesda, MD, 2009.

[85] Green D, Roberts PR, New DI, Kalra PA. Sudden cardiac death in hemodialysis patients: an in-depth review. Am J Kidney Dis. 2011; 57(6):921-929. doi:10.1053/j.ajkd.2011.02.376.

[86] Bleyer AJ, Russell GB, Satko SG. Sudden and cardiac death rates in hemodialysis patients. Kidney Int. 1999; 55(4):1553-1559. doi:10.1046/j.1523-1755.1999.00391.x.

[87] Perl J., Chan C.T. Timing of sudden death relative to the hemodialysis procedure. Nat Clin Pract Nephrol. 2006; 2(12):668-669. doi:10.1038/ncpneph0345.

[88] Bauer A, Watanabe MA, Barthel P, et al. QRS duration and late mortality in unselected postinfarction patients of the revasculation era. Eur Heart J. 2006; 27(4):427-433. doi:10.1093/eurheartj/ehi683

[89] Block GA, Klassen PS, Lazarus JM, et al. Mineral metabolism, mortality and morbidity in maintenance hemodialysis. J Am Soc Nephrol. 2004; 15(8):2208-2218. doi:10.1097/01.ASN.0000133041.27682.A2

[90] Faul C, Amaral AP, Oskouei B, et al. FGF23 induces left ventricular hypertrophy. J Clin Invest. 2011; 121(11):4393-4408. doi:10.1172/JCI46122.

[91] Xie J, Yoon J, An SW, Kuro-o M, Huang CL. Soluble Klotho protects against uremic cardiomyopathy independently of fibroblast growth factor 23 and phosphate. J Am Soc Nephrol. 2015; 26(5):1150-1160. doi:10.1681/ASN.2014040325.

[92] Hyperphosphataemia in chronic kidney disease. Management of hyperphosphataemia in patients with stage 4 or 5 chronic kidney disease. National Institute for Health and Clinical Excellence (UK). NICE clinical guideline No 157; March 2013.

[93] Shanahan CM, Crouthamel MH, Kapustin A, Giachelli CM. Arterial calcification in chronic kidney disease: key roles for calcium and phosphate. Circ Res. 2011; 109(6):697-711. doi:10.1161/CIRCRESAHA.110.234914.

[94] Mizobuchi M, Towler D, Slatopolsky E. Vascular calcification: the killer of patients with chronic kidney disease. J Am Soc Nephrol. 2009; 20(7):1453-1464. doi:10.1681/ASN.2008070692.

[95] Guérin AP, London GM, Marchais SJ, Metivier F. Arterial stiffening and vascular calcifications in end-stage renal disease. Nephrol Dial Transplant. 2000; 15(7):1014-1021. doi:10.1093/ndt/15.7.1014.

[96] Toussaint ND, Kerr PG. Vascular calcification and arterial stiffness in chronic kidney disease: implications and management. Nephrology (Carlton). 2007; 12(5):500-509. doi:10.1111/j.1440-1797.2007.00823.x.

[97] Van den Bergh G, Opdebeeck B, D'Haese PC, Verhulst A. The vicious cycle of arterial stiffness and arterial media calcification. Trends Mol Med. 2019; 25(12):1133-1146. doi:10.1016/j.molmed.2019.08.006.

[98] Rong S, Qiu X, Jin X, et al. Risk factors for heart valve calcification in chronic kidney disease. Medicine (Baltimore). 2018; 97(5):e9804. doi:10.1097/MD.0000000000009804

[99] Raggi P. Cardiovascular disease: Coronary artery calcification predicts risk of CVD in patients with CKD. Nat Rev Nephrol. 2017; 13(6):324-326. doi:10.1038/nrneph.2017.61.

[100] Gauthier-Bastien A, Ung RV, Larivière R, et al. Vascular remodeling and media calcification increases arterial stiffness in chronic kidney disease. Clin Exp Hypertens. 2014; 36(3):173-180. doi:10.3109/10641963.2013.804541.

[101] Sprague SM. A comparative review of the efficacy and safety of established

phosphate binder: calcium, sevelamer, and lanthanum carbonate. Curr Med Res Opin. 2007; 23(12):3167-3175. doi:10.1185/030079907X242719

[102] Patel L, Bernard LM, Elder GJ. Sevelamer versus calcium-based binders for treatment of hyperphosphatemia in CKD: a meta-analysis of randomized controlled trials. Clin J Am Soc Nephrol. 2016; 11(2):232-244. doi:10.2215/CJN.06800615

[103] Floege J, Covic AC, Ketteler M, et al. A phase III study of the efficacy and safety of a novel iron-based phosphate binder in dialysis patients. Kidney Int. 2014; 86(3):638-647. doi:10.1038/ki.2014.58

[104] Komaba H, Taniguchi M, Wada A, et al. Parathyroidectomy and survival among Japanese hemodialysis patients with secondary hyperparathyroidism. Kidney Int. 2015; 88(2):350-359. doi:10.1038/ki.2015.72

[105] Chertow GM, Block GA, Correa-Rotter R, et al; EVOLVE Trial Investigators. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. New Engl J Med. 2012; 387(26):2482-2494. doi:10.1056/NEJMoa1205624

[106] Wheeler DC, London GM, Parfrey PS, et al; EValuationOf Cinacalcet HCl Therapy to Lower Cardio Vascular Events (EVOLVE) Trial Investigators. Effects of cinacalcet on atherosclerotic and nonatherosclerotic cardiovascular events in patients receiving hemodialysis: the evaluation of cinacalcet HCL therapy to lower cardiovascular events (EVOLVE) trial. J Am Heart Assoc. 2014; 3(6):e001363. doi:10.1161/JAHA.114.001363

[107] Chung DR, Huh K. Novel pandemic influenza A (H1N1) and community associated methicillin resistant Staphylococcus aureus pneumonia. Expert Rev Anti Infect Ther. 2015; 13(2):197-207. doi:10.1586/14787210.2015.999668

[108] Moreillon P, Que YA. Infective endocarditis. Lancet. 2004; 363(9403):139-149. doi:10.1016/S0140-6736(03)15266-X

[109] Fowler VG, Miro JM, Hoen B, et al. Staphylococcus aureus endocarditis: a consequence of medical progress. JAMA. 2005; 293(24):3012-3021. doi:10.1001/jama.293.24.3012

[110] Ezekowyz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with pooroutcomes: insights from a cohort of 12 065 patients with new-onset heart failure. Circulation. 2003; 107(2): 223-225. doi:10.1161/01.cir.0000052622.51963.fc

[111] Philipp S, Ollmann H, Schimk T, et al. The impact of anemia and kidney function in congestive heart failure and preserved systolic function. Nephrol Dial Transplant. 2005; 20(5):915-919. doi:10.1093/ndt/gfh753

[112] Fishbane S. Erythropoiesis-stimulating agent treatment with full anemia correction: a new perspective. Kidney Int. 2009; 75(4):358-365. doi:10.1038/ki.2008.467

[113] Haase VH. Hypoxia-inducible factor-prolyl hydroxylase inhibitors in the treatment of anemia of chronic kidney disease. Kidney Int Suppl (2011). 2021; 11(1):8-25. doi:10.1016/j.kisu.2020.12.002

[114] Nakhoul F, Yigla M, Gilman R, Reisner SA, Abassi Z. The pathogenesis of pulmonary hypertension in haemodialysis patients via arterio-venous access. Nephrol Dial Transplant. 2005; 20(8):1686-1692. doi:10.1093/ndt/gfh840

[115] Von Bibra H, Castro L, Autenrieth G, McLeod A, Gurland HJ.

The effects of arteriovenous shunts on cardiac function in renal dialysis patients – an echocardiographic evaluation. Clin Nephrol. 1978; 9(5):205-209. PMID:657597

[116] Yigla M, Nakhoul F, Sabag A, et al. Pulmonary hypertension in patients with end-stage renal disease. Chest. 2003; 123(5):1577-1582. doi:10.1378/chest.123.5.1577

[117] Clarkson MR, Giblin L, Brown A, Little D, Donohoe J. Reversal of pulmonary hypertension after ligation of a brachiocephalic arteriovenous fistula. Am J Kidney Dis. 2002; 40(3):E8. doi:10.1053/ajkd.2002.34932

[118] Yigla M, Abassi Z, Reisner SA, Nakhoul F. Pulmonary hypertension in hemodialysis patients: an unrecognized threat. Semin Dial. 2006; 19(5):353-357. doi:10.1111/j.1525-139X.2006.00186.x

[119] Crowley SD, Butterly DW, Peter RH, Schwab SJ. Coronary steal from a left internal mammary artery coronary artery bypass graft by a left upper extremity ateriovenous hemodialysis fistula. Am J Kidney Dis. 2002; 40(4):852-855. doi:10.1053/ajkd.2002.35701