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REVIEW ARTICE

Myocardial infarction in hemodialysis patients

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Abstract

The review provides data on risk factors of the development of acute myocardial infarction in patients with end-stage chronic kidney disease, including hemodialysis patients. The role of traditional, specific "renal" and dialysis-related risk factors for the development of acute myocardial infarction in patients undergoing hemodialysis is discussed. The role of hyperphosphatemia, hyperuricemia, anemia, oxidative stress, inflammation and endothelial dysfunction in the occurrence of cardiac events is also considered. The clinical significance of intra-and interdialytic hypotension as potential factor predisposing for the development of acute myocardial infarction is highlighted. We also focused attention on the assessment of cardiac troponin I level in the diagnosis of acute myocardial infarction in hemodialysis patients.

Key words: *myocardial infarction, hemodialysis, intradialytic hypotension, troponin I.*

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In 2002 the research group led by Andrew S. Levey presented clinical guidelines for the treatment of chronic kidney disease (CKD in the American Journal of Kidney Diseases) [1]. CKD is defined as kidney damage and / or impaired kidney function for over three months, regardless of origin [1]. Markers of kidney damage include albuminuria / proteinuria, erythrocyturia, and decreased glomerular filtration rate (GFR)<60 ml/min/1.73 m^2 is considered as indicator of decreased renal function [1]. The division of CKD into five stages is based on the degree of GFR reduction, where the fifth corresponds to the terminal stage of CKD [2]. The international guidelines from 2014 emphasize the division of CKD stage 3 into 2 substages by GFR value — 3A (GFR from 59 to 45 ml/min/1.73 m^2) and 3B (GFR from 44 to 30 ml/min/1.73 m^2) [3]. Authors claim that renal and cardiovascular prognosis are different in these subgroups [3]. Thus, patients with stage 3A CKD have high cardiovascular risk and moderate rates of CKD progression, and patients with stage 3B CKD have higher risk of end-stage renal failure compared with fatal cardiovascular complications (CVC) [3]. On the other hand, patients with CKD, regardless of the stage of pathological process, belong to the group with high cardiovascular risk [3].

In recent years, the relevance of the studies on CVC in patients with CKD has increased due to higher incidence, severity of the course, the presence of complications and disability. According to A.G. Strokova et al. (2017) approximately 80 % of patients with end-stage CKD are on programmed hemodialysis (HD) [4]. In Kyrgyzstan, the population of patients with stage 5 "D" of CKD is over half thousand people [5]. Many studies have noted that in patients with end-stage CKD, cardiovascular complications account for at least one third of all admissions and about 43–50 % of all deaths [6]. 20 % of all deaths in patients with end-stage CKD cis caused by acute myocardial infarction (AMI) [7]. Recent publications report that by the start of renal replacement therapy (RRT), coronary heart disease is detected in about 40 % of patients [8]. C.A. Herzog et al. (2007) showed that AMI develops by the end of the first year of RRT in 30 % of patients, and by the end of the second year — in 52 % [7]. This study also showed that during the first year, the mortality rate from AMI in patients with end-stage CKD reaches 59 %, by the end of the second year — 74 % [6]. In CKD, regardless of the GFR value, the risk of AMI development increases, but it is even higher in patients on programmed HD [3]. It is important to emphasize the fact that in-hospital mortality from AMI among patients on HD is 30 %, and in patients with normal renal function — 2 % [9]. Therefore, in patients with unstable hemodynamics and multiple lesions of the coronary arteries, myocardial revascularization is highly recommended. It should be noted that X-ray imaging is an important step in the diagnosis and treatment of such patients [7].

Risk factors for the development of acute myocardial infarction in patients on programmed hemodialysis

As indicated above, patients on programmed HD have a high risk of AMI [3]. Similar to other countries [1,3], in Russia most patients with type 2 diabetes mellitus and arterial hypertension are undergoing HD [5]. In most cases these patients belong to older age group. At the same time, the incidence of comorbidities increases with age, and atherosclerosis of coronary arteries is observed more frequently in older patients. It is also remarkable that the duration of HD therapy not only accelerates systemic atherosclerosis, but also causes structural changes in blood vessels. In addition, specific "renal" risk factors for CVC become more pronounced in patients with CKD during HD (Table 1).

Hyperphosphatemia

Patients on HD have consistently high blood phosphorus levels (over 1.45 mmol/L) that increases the fre-

Table 1. **Risk factors for acute myocardial infarction development in patients on HD**

Traditional risk factors	Specific "renal" risk factors	Factors associated with dialysis therapy
Age, smoking, arterial hypertension, hypercholesterolemia, dyslipidemia, obesity, diabetes mellitus, hereditary predisposition, etc.	Decreased glomerular filtration rate, hyperphosphatemia, anemia, hyperuricemia, inflammation, oxidative stress, endothelial dysfunction.	The duration of dialysis therapy, intra- and interdialytic arterial hypotension.

quency of CVC [10]. Hyperphosphatemia accelerates the calcification of coronary arteries, causes systemic inflammation, oxidative stress, and promotes vascular calcification of the media in patients undergoing programmed HD [11]. M. Tagawa et al. (2014) studied the association between phosphate, calcium, intact parathyroid hormone and composite cardiovascular endpoints, including AMI [12]. The authors of the Japan Renal Data Registry included 65,849 patients on programmed HD in the study. The endpoint was the first episode of AMI or cerebral stroke during 1-year follow-up [12]. AMI was recorded in 1048 patients with end-stage CKD who underwent programmed HD [12]. The frequency of hemorrhagic and ischemic strokes was 651 and 2089 cases, respectively. The risk of AMI development was associated with phosphate level≥6.5 mg/dL (odds ratio, 1.49; CI, 1.23–1.80) [12]. Another study noted that the increased of blood phosphorus for every 1 mg/dL increases the mortality by 18% [13]. Hyperphosphatemia in patients on programmed HD impairs the compliance and increases stiffness of the arteries. Data on the association between hyperphosphatemia and calcification of coronary arteries were obtained in two large population studies [14,15]. The MESA study (MultiEthnic Study of Atherosclerosis) showed the association between hyperphosphatemia and calcification of coronary arteries in young and middle-aged patients with CKD with normal renal function. For every 1 mg/dL increase of serum phosphorus, the risk of coronary arteries calcification increased by 21% [15]. Impaired phosphorus-calcium metabolism causes endothelial dysfunction accompanied by increased lipid peroxidation and oxidative stress that increases the risk of AMI. The accumulation of calcium in smooth muscle cells and subsequent calcification of coronary arteries in patients undergoing programmed HD is considered one of the most significant factors in the pathogenesis of CVC [14].

Hyperuricemia

The increase of blood uric acid>0.42 mmol/L in men and>0.36 mmol/L in women is an independent risk factor of CVC in patients on programmed HD [1]. Persistent hyperuricemia in patients with CKD can be a predictor of myocardial ischemia and increases the risk of AMI by 4% [16]. The concentration of uric acid increases in coronary arteries during hypoxia due to temporary occlusion of the vessel [17]. Hyperuricemia in patients on programmed HD together with other factors enhances chronic inflammation, athero- and thrombogenesis. Nowadays the role of hyperuricemia in the development of CVC in patients on programmed HD is controversial [18], although elevated uric acid levels in CKD are also associated with other cardiovascular risk factors. The British Regional Heart Study included 7688 people aged from 40 to 59 years, and showed the association between elevated uric acid levels and fatal and non-fatal manifestations of coronary heart disease [19]. With every 1 mg/dL increase of uric acid level, the risk coefficient of coronary heart disease mortality in women increased up to 1.48 mg/dL [20]. According to other data, the difference of uric acid level of 1.45 mg/dL increases the risk of CVC by 22% [21].

Anemia and oxidative stress

Anemia is a common complication of CKD that can develop in patient with all types of HD. Thus, in the absence of treatment, the level of hemoglobin less than 100 g/l is observed in over 90% of patients [22]. Low hemoglobin level can serve as extracardiac factor that increases myocardial ischemia. Hypoxic vasodilation increases the activity of the sympathetic nervous system and causes tachycardia and increases venous return that can lead to a matched increase in cardiac output [22]. At the same time anemia is associated with high fibrinogen and C-reactive protein blood levels. Persistent anemia increases oxidative stress that also negatively affects the state of the cardiovascular system [22]. It is also remarkable that low hemoglobin level decreases coronary flow reserve [23]. In patients on HD, anemia increases arterial blood flow velocities, leads to the thickening of large arteries walls and decreased arterial compliance, increases peak systolic blood pressure (BP), stroke volume and cardiac output and, therefore, contributes to the development of AMI [22]. The results of researches have shown that the decrease in hemoglobin level of 4–5 g/l affects the prognosis of CVC and, therefore, requires correction [23].

Many researchers note that the HD session is associated with the development of oxidative stress, because during the contact with the dialysis membrane, leukocytes (neutrophils, monocytes) activates and lead to excessive production of reactive oxygen species, such as superoxide radical anion (O_2), H_2O_2, hydroxyl radical through complement-dependent and complement-independent mechanisms [24]. The severity of oxidative stress is influenced by the biocompatibility of the dialysis membrane [25]. During the uremia, the antioxidant reserve is reduced,

which, in particular, is expressed as increased ratio of oxidized glutathione / reduced glutathione in blood plasma [25]. When patient additionally have anemia, it initiates oxidative modification of low-density lipoproteins, proteins, activates phospholipases and oxidative stress is aggravated that contributes to destabilization of atherosclerotic plaques and the development of AMI. Moreover, even a single HD session enhances lipid peroxidation and reduces the level of antioxidants [25].

Inflammation and endothelial dysfunction

The association between endothelial dysfunction and inflammation manifests by both general triggering stimuli and complex of cellular and humoral factors that mediate their pathogenesis and also serve as markers of these conditions, factors for further damage of endothelium and the development of endothelial dysfunction [26]. A number of authors noted the association between systemic inflammation and the level of nitric oxide. Other factors also play an important role in the pathogenesis of coronary atherosclerosis: impaired coronary autoregulation with atherosclerosis and calcification of the arterial endothelium, anemia, oxidative stress, dyslipidemia, and increased levels of C-reactive protein [27]. The development of AMI in patients with CKD who are on programmed HD is associated not only with the destabilization of atherosclerotic plaque and thrombus formation, but also with the inflammation of vessel's wall [3]. Patients with anemia and end-stage CKD more frequently have increased C-reactive protein compared with patients without CKD. Moreover, almost all dialysis-dependent patients who had AMI, showed increased level of C-reactive protein [25]. In addition, programmed HD activates lipid peroxidation processes that damaged membrane lipids, inactivates SH-groups of proteins, impairs cell division and phagocytosis, and, therefore, leads to change in the structural and functional organization of membranes [25,26].

Intra- and interdialytic arterial hypotension

Decreased BP induced by HD increases the risk of AMI through the activation of sympathetic nervous system, increases or decreases heart rate, which, in case of severe calcification of coronary arteries, leads to myocardial hypoxia, as well as complications from permanent vascular access — arteriovenous fistula thrombosis [28,29]. The prevalence of intradialytic arterial hypotension ranges from 10 to 50%, and mortality rate due to decreased blood pressure during the HD procedure can reach 10–15% per year [30]. The meta-analysis by J. Kuipers et al. (2019) showed that the prevalence of HD sessions complicated by intradialytic arterial hypotension does not exceed 12% [31]. The main risk factors associated with intradialytic arterial hypotension in different studies included diabetes mellitus, high weight gain, female sex and low body weight [31]. It is assumed that the level of calcium in coronary arteries is associated with decreased blood pressure during the HD procedure in patients with end-stage CKD [28,29]. Many patients on HD with prolonged intradialytic arterial hypotension develop silent myocardial ischemia, which increases the risk of AMI and life-threatening cardiac arrhythmias [28,29].

The diagnosis of AMI in patients on hemodialysis

According to A.Yu. Nikolaev, the diagnosis of painless and arrhythmic forms of AMI causes certain difficulties in patients on HD, especially among people with diabetic nephropathy and autonomic neuropathy [32]. Patients on HD often have stenosis of the proximal coronary arteries that causes AMI [32]. F.I. Belyalov points out that patients with end-stage CKD less often have AMI that manifest with pain in the chest, arm and neck, elevation of the ST segment on the electrocardiogram (ECG), and more often — shortness of breath and symptoms of heart failure. The absence of pain syndrome can be explained by decreased threshold of pain receptors, increased left ventricular myocardial mass, and imbalanced autonomic regulation of cardiac activity. In addition, it should also be noted that electrolyte imbalance, especially during HD sessions, can lead to changes in the terminal portion of the QRS complex that can reduce the diagnostic value of ECG studies in this category of patients [33]. Therefore, echocardiographic study in patients on programmed HD have high diagnostic value. Thus, the detection of hypo- and akinetic zones of ventricular myocardium in the absence of bundle branch block and atrial fibrillation in patients on programmed HD can be interpreted as AMI [34].

The important step is the identification of highly sensitive troponin I, since it rarely rises even in patients with end-stage CKD without myocardial ischemia. Due to kinetics, troponin T and troponin I respond differently to renal function changes [35,36]. The level of troponin T in patients with renal failure

can increase up to 17–53 %, troponin I — up to 7 %. After the HD session, the troponin T level increases in 86 % of cases, when the troponin I level decreases [6]. In patients on programmed HD, the diagnosis of AMI should be based on all classical criteria — clinical, ECG and laboratory biomarkers. The high incidence of atypical AMI manifestations in these patients leads to underdiagnosis and inappropriate treatment. In patients on programmed HD AMI often manifests as shortness of breath that can be interpreted as volume overload. The M.Yu. Gilyarova (2019) showed that in patients with AMI symptoms, the level of troponin should be assessed within 3–6 hours [8]. The researchers point out that the level of troponin above the 99th percentile and its change by over 20 % is the criterion for the diagnosis of AMI in patients with CKD. It should also be noted that HD affects the level of cardiac biomarkers. Their level may increase due to hemoconcentration or decrease due to clearance or binding to the dialysis membrane. The assessment of dynamic changes of troponin levels increases the diagnostic accuracy. Meanwhile, if relying only on the level of troponin, up to 12 % of cases of ST segment elevation AMI can be skipped [8].

Conclusion

Thus, the presented data indicate hyperphosphatemia, hyperuricemia, anemia and oxidative stress, inflammation, and endothelial dysfunction play a pivotal role in the development of AMI in patients undergoing programmed HD. An additional risk factor for AMI is frequent and prolonged episodes of intradialytic arterial hypotension. The diagnosis of AMI in patients with the terminal stage of CKD and on programmed HD is based on the dynamic assessment of ECG parameters and the levels of cardiac troponins. Many issues of pathogenesis and treatment of AMI in patients with CKD on programmed HD need further clarification.

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References

1. Levey A.S., Coresh J., Bolton K., et al. National Kidney Foundation. K/DOQI Clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis.2002;39:2(Suppl 1): SI-266.
2. Dudko M.Yu., Kotenko O.N., Malkoch A.V. Role of population screening in identication of chronic kidney disease. Lechaschi Vrach. 2019;1:50–52. Russian.
3. Moiseev V.C., Mukhin N.A. Cardiovascular risk and chronic kidney disease: cardio- and nephroprotection strategies. Clinical nephrology.2014;2:4–29. Russian.
4. Strokov G.A., Gurevich K.Y., Ilyin A.P., et al. Treatment of patients with chronic kidney disease stage 5 (CKD 5) by hemodialysis and hemodiafiltration. Clinical guidelines. Nephrology (Saint-Petersburg). 2017;21(3): 92–111. Russian.
5. Murkamilov I.T. The prevalence, clinical and functional characteristics of chronic kidney disease in residents of urban and rural areas in the Kyrgyz Republic. Clinical nephrology.2019;4:5–10. Russian.
6. Zhuravkov Y.L., Koroleva A.A. Some features of diagnostics and treatment of the acute coronary syndrome at chronic illness of kidneys. Military medicine. 2015;4(37): 132–136. Russian.
7. Herzog C.A., Littrell K., Arko C., et al. Clinical characteristics of dialysis patients with acute myocardial infarction in the United States: a collaborative project of the United States Renal Data System and the National Registry of Myocardial Infarction. Circulation 2007; 116:13:1465–1672.
8. Antukh D.E., Shchekochikhin D.Yu., Nesterov A.P., Gilarov M Yu. Diagnosis and treatment of myocardial infarction in patient with end-stage renal disease on chronic hemodialysis. Therapeutic Archive. 2019;91(6): 137–144. Russian.
9. Wright R.S., Reeder G.S., Herzog C.A., et al. Acute myocardial infarction and renal dysfunction: a high-risk combination. Annals of internal medicine.2002;137:7:563–570.
10. Martynov S.A., Shamkhalova M.Sh. Hyperphosphatemia in chronic kidney disease. Meditsinskiy sovet. 2019;16:78–85. https://doi.org/10.21518/2079–701X-2019–16-78–85. Russian.
11. Milovanov Yu.S., Fomin V.V., Milovanova L.Yu. Difficulties in correcting hyperphosphatemia in patients with chronic renal failure. A place of noncalcium-containing phosphate-binding drugs. Therapeutic archive.2016; 88(6): 95–100. Russian.
12. Tagawa M., Hamano T., Nishi H., et al. Mineral metabolism markers are associated with myocardial infarction and hemorrhagic stroke but not ischemic stroke in hemodialysis patients: a longitudinal study. PloS one.2014;9:12.e114678.
13. Kestenbaum B., Sampson J.N., Rudser K.D., et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. J. Am. Soc. Nephrol.2005;16:520–528.
14. Foley R.N., Collins A.J., Herzog C.A., et al. Serum phosphorus levels associate with coronary atherosclerosis in young adults.J. Am. Soc. Nephrol. 2009;20:397–404.
15. Robinson-Cohen C., Shlipak M., Sarnak M., et al. Impact of race on the association of mineral metabolism with heart failure: the Multi-Ethnic Study of Atherosclerosis.The Journal of Clinical Endocrinology & Metabolism. 2020; 105: 4: e1144-e1151.
16. Krishnan E., Baker J.F., Furst D.E., Schumacher H.R. Gout and the risk of acute myocardial infarction. Arthritis Rheum.2006;54:2688–2696.

17. Hur I., Choi S.J., Kalantar-Zadeh K. Serum uric acid and mortality risk among maintenance hemodialysis patients. Kidney research and clinical practice. 2017;36:4:302–304.
18. Kim C.S., Jin D.C., Yun Y.C., et al. Relationship between serum uric acid and mortality among hemodialysis patients: Retrospective analysis of Korean end-stage renal disease registry data. Kidney Res Clin Pract. 2017;36:368–376.
19. Wannamethee S.G., Shaper A.G., Whincup P.H. Serum urate and the risk of major coronary heart disease events. Heart.1997;78:2:147–153.
20. Freedman D.S., Williamson D.F., Gunter E.W., Byers T. Relation of serum uric acid to mortality and ischemic heart disease: the NHANES I Epidemiologic Follow-up Study. American journal of epidemiology. 1995;141:637–644.
21. Alderman M.H., Cohen H., Madhavan S., Kivlighn S. Serum uric acid and cardiovascular events in successfully treated hypertensive patients. Hypertension.1999;34:1:144–150.
22. Abramovitz B., Berns J.S. Management of Anemia in Chronic Kidney Disease. Chronic Renal Disease. Academic Press.2020. C. 991–1000.
23. Abdullaeva S.Ya., Nikishin A.G., Pirnazarov M.M., et al. Anemia of chronic disease as a risk factor in patients with coronary artery disease and lesion of the left main coronary artery. Eurasian heart journal. 2017;25;2:14–19. Russian.
24. Susla A.B., Mysula I.R., Gozhenko A.I. The effect of hemodialys on endothelial dysfunction in patients with end-stage renal disease. Klin. med. 2017;95(10): 935–939. Russian.
25. Saenko Yu.V., Shutov A.M. The impact of oxidative stress on cardiovascular pathology in patients with kidney diseases (Part II. Clinical aspects of oxidative stress). Nephrology and Dialysis. 2004;2:6:138–144. Russian.
26. Belaya I.E. The markers of oxidative stress in patients with acute myocardial infarction with non-alcoholic fatty liver disease. Russian Journal of Cardiology. 2014;(7): 98–104. Russian.
27. Tabriziani H., Baron P., Abudayyeh I., Lipkowitz M. Cardiac risk assessment for end-stage renal disease patients on the renal transplant waiting list.Clinical Kidney Journal.2019;12:4:576–585.
28. Jeon H.J., Oh J., Lee Y.K., et al. Static intra-access pressure ratio and cardiovascular events in patients undergoing haemodialysis.Scientific reports.2020;10:1:1–8.
29. Yeo S., Moon J.I., Shin J., et al. Impacts of Coronary Artery Calcification on Intradialytic Blood Pressure Patterns in Patients Receiving Maintenance Hemodialysis. Chonnam Medical Journal.2020;56:1:27–35.
30. Tisler A., Akocsi K., Fazakas L., et al. The effect of frequent or occasional dialysis-associated hypotension on survival of patients on maintenance haemodialysis. Nephrol Dial Transplant. 2003;18(12): 2601–2605.
31. Kuipers J., Verboom L.M., Ipema K.J., et al. The prevalence of intradialytic hypotension in patients on conventional hemodialysis: A systematic review with meta-analysis. American journal of nephrology.2019;49:6:497–506.
32. Nikolaev A.Yu., Milovanov Yu.S. Treatment of renal failure. A guide for doctors. 2nd ed. M.: Medical News Agency, 2011.P.592. Russian.
33. Belyalov F.I. Acute coronary syndrome and renal dysfunction. Rational Pharmacotherapy in Cardiology.2016;12(1): 72–78. Russian.
34. Mardanov B.U., Mamedov M.N., Korneeva M.N., Oganov R.G. Features of the in-hospital course of myocardial infarction in patients with glucose metabolism disorders. Rational Pharmacotherapy in Cardiology. 2015;11(5): 477–482. Russian.
35. Kuo P.Y., Saran R., Argentina M., et al. Cramping, crashing, cannulating, and clotting: a qualitative study of patients definitions of a "bad run" on hemodialysis. BMC nephrology.2020;21:1:1–10.
36. Sedykh D.Yu., Chesnokova L.Yu., Kashtalap V.V., et al. Challenges in treating hemodialysisdependent patients with acute myocardial infarction. A clinical case. Complex Issues of Cardiovascular Diseases. 2019;8(2): 135–142. Russian.