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Stroke risk factors in patients with end-stage kidney disease: current status of the problem

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Abstract

Chronic kidney disease and its complications are one of the leading causes of morbidity, disability and mortality in the world population, due to both the widespread prevalence of arterial hypertension, diabetes mellitus and coronary heart disease, and the increase in life expectancy. In the terminal stage of chronic kidney disease, mortality from cardiovascular events increases significantly. This review examines the most common risk factors for stroke in end-stage kidney disease. The role of arterial hypertension, diabetes mellitus, chronic heart failure is discussed, taking into account common risk factors, hyperactivation of the renin-angiotensin-aldosterone system, the development of oxidative stress, volume overload with an increase in the size of the left atrium and a subsequent increase in the risk of thrombosis and stroke in patients with end-stage kidney disease on programmed hemodialysis. In addition, data are presented in the study of the contribution of bone mineral disorders to the occurrence of cerebral complications in this category of patients. Timely diagnosis of cardiovascular diseases and secondary prevention of stroke, including adequate antihypertensive, hypoglycemic therapy and correction of heart failure with blockers of the renin-angiotensin-aldosterone system, as well as the elimination of bone mineral disorders are currently a very popular approach to improving the quality of life and increased survival in the discussed category of patients. Understanding the pathogenetic mechanism of stroke in patients with end-stage kidney disease on programmed hemodialysis, with the study of risk factors in the development of an acute cerebrovascular accident, will help to develop a strategy for their management.

Keywords: renal failure, stroke, risk factors, secondary prevention.

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Introduction. Chronic kidney disease (CKD) and its complications represent one of the leading causes of morbidity, disability, and mortality in populations worldwide, which is due to both the widespread prevalence of hypertension (HT), diabetes mellitus (DM), and coronary heart disease and the increase in life expectancy of individuals [1].

The consideration of different renal and cardiovascular prognoses in CKD led to the subdivision of stage 3 CKD into 3A [range of glomerular filtration rate (GFR): 59–45 ml/min/1.73 m^2] and 3B (GFR range: 44–30 ml/min/1.73 m^2). In stage 3A CKD, a high cardiovascular risk is recorded with a moderate CKD progression rate; however, in patients with stage 3B CKD, the risk of end-stage renal failure is higher than the risk of fatal cardiovascular complications [2].

Cardiovascular events have become the main cause of death in CKD patients, while damage and/or decreased renal function are significant cardiovascular risk factors [1,2]. It has been shown that death due to cardiovascular complications is

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several times more common in patients with end-stage CKD [1,2]. Left ventricular hypertrophy, myocardial infarction, chronic heart failure (CHF), atrial fibrillation, and cerebral strokes are common cardiovascular complications in patients with end-stage CKD [3].

It should be noted that additional (specific) risk factors for the occurrence of cardiovascular complications appear in end-stage CKD and at the renal replacement therapy stage [4]. Currently, the role of HT, DM, CHF, and bone mineral disorders as potential risk factors for stroke in dialysis-dependent patients is being discussed [4,5], that is, the disease etiology is thought to be multifactorial [6,7]. In this light, we hope that our analysis of the literature data on the role and place of risk factors for stroke in patients with end-stage CKD who receive programmed hemodialysis (HD) will be useful to solve the issues related to the management of this group of patients.

Hypertension. A close relationship between increased blood pressure (BP) and end-stage CKD has been noted by many researchers [1,2]. The association of HT, CKD, and stroke is due to the presence of common risk factors and mechanisms that are involved in the development of these pathological conditions [1]. In end-stage CKD, almost one of every two patients is diagnosed with HT, which is often resistant to antihypertensive therapy [3]. The achievement of the target BP level by the start of the renal replacement therapy provides a better survival rate and quality of life with the programmed HD [8]. HT is recorded in more than half of patients who have had acute cerebrovascular accidents (ACVA) [9], while antihypertensive therapy is accompanied by a 19% decrease in the relative risk of recurrent stroke [10].

A retrospective study by D. Timofte et al. (2020) in a group of 109 patients with stage 5 CKD at the start of renal replacement therapy revealed the presence of HT in 85.32% of patients and a history of stroke in 13.76% of cases [8]. A high prevalence of HT was also revealed according to the results of the cohort study by Y.R.Humudat et al. (2019), in which the presence of high BP was recorded in 77% of 320 dialysis-dependent patients [11]. Similar results were obtained by other researchers who reported that approximately 80% (72%–88%) of patients on programmed HD have HT [12]. Concurrently, in 10%–15% of patients with end-stage CKD, an intradialysis BP decrease was recorded, which additionally contributes to the occurrence of stroke [12].

The restructuring of extra- and intracranial arteries due to the persistent increase in BP can be a leading factor in the pathogenesis of strokes in end-stage CKD. Microangiopathy of cerebral vessels aggravates metabolic disorders that develop during HT, atherosclerosis, and vascular calcification, and increases the risk of asymptomatic strokes [13]. The results of clinical studies indicate that ACVA in end-stage CKD often develops in the presence of increased BP, and is frequently accompanied by consciousness disorders and neurologic impairment [14]. As a rule, areas of cerebral infarctions are formed in this group of patients, and in most cases, the recovery process is slow and incomplete. Progressive cognitive impairments have also been found to be frequent complications of ACVA in patients on programmed HD, which reduces the patients' adherence to dialysis therapy and creates certain difficulties for the medical staff of the dialysis department [15].

Thus, HT and the development of lesions of target organs, including the vascular wall, are risk factors for the occurrence of strokes in end-stage CKD, and appropriate antihypertensive therapy can reduce the relative risk of ACVA.

Diabetes mellitus. The proportion of diabetic nephropathy among patients with end-stage CKD is 23%–39% by the start of the renal replacement therapy [8,9]. In a retrospective study, S.D.Pande and J.Morris (2020) showed that among 37 patients in the pre-dialysis and dialysis stages of CKD, DM was found in 27 (73%) patients, and ischemic stroke was observed in 34 (91.8%) patients [16].

In Kyrgyzstan, type 2 DM ranks second as the cause of end-stage renal failure after HT [17]. The negative effect of chronic hyperglycemia on the central nervous system and kidneys is due to the fact that there is an excessive formation of intermediate and end products of glycation. This leads to inflammatory processes, damage to the vascular wall, endothelial dysfunction, and impaired blood flow in the capillaries [3].

The incidence of stroke among patients with type 2 DM is 4–7 times higher than in the general population [18] because all the three structural and functional levels of the cerebral vascular system (main arteries of the head, which are the target of the atherosclerotic process; intracranial perforating vessels, which become the object of HT; microvasculature, where dysmetabolic processes develop) are accompanied by oxidative stress and endothelial dysfunction under conditions of damage to the blood-brain barrier [19]. Chronic hyperglycemia accelerates the remodeling of cerebral vessels as a result of atherosclerosis and increases the risk of impaired cognitive functions and vascular dementia even before organic damage to the central nervous system occurs. Moreover, significant risk factors for Alzheimer's disease are also noted in patients with type 2 DM [19].

In a retrospective assessment of the incidence of stroke in 195 patients with end-stage CKD of diabetic etiology on programmed HD, Y. Shinya et al. (2020) observed the presence of stroke in 41 (21%) patients [20], and the incidence of ACVA per 1,000 patient-years was 53.6. Multivariate analysis demonstrated that CKD of diabetic etiology is a significant risk factor for stroke (risk ratio, 2.63; 95% confidence interval, 1.08–7.85; $p = 0.032$) [20].

J. Stamler et al. (1993) established that the relative risk of stroke in patients with type 2 DM is 1.8–6 times higher than that in patients without DM [21]. In the MRFIT study (The Multiple Risk Factor Intervention Trial), the risk of death from stroke among DM patients was 2.8 times higher than in patients without DM; specifically, the risk of death from ischemic stroke was 3.8 times higher, and that from hemorrhagic stroke was 1.5 times higher [21].

Arterial calcification complicating the course of CKD has been found to be a risk factor for stroke. It should be noted that in type 2 DM, a lesion of the tunica media of the arteries is revealed (Monckeberg's sclerosis) [22]. Calcification of the tunica media of the arterial walls in patients with type 2 DM is also associated with distal symmetric neuropathy [23].

End-stage CKD is a recognized risk factor of prolonged hypoglycemia. It should be noted that glucose has a toxic effect not only in hyperglycemia, but also in hypoglycemic conditions, as well as with variability in glucose levels [24]. It is known that, starting from the pre-dialysis stages of CKD, frequent episodes of hypoglycemia occur in patients with type 2 DM, and this is accompanied by an increase in renal and cerebrovascular risks.

The sympathetic nervous system reacts to the development of severe hypoglycemia by increasing the level of catecholamines, which leads to the activation of platelets and leukocytes and is accompanied by an increased risk of the destabilization of atherosclerotic plaques, including those in the carotid arteries, as well as a disorder of energy metabolism in the brain. Inflammation and endothelial dysfunction, as a response to acute hypoglycemia, are significant in the development of atherosclerosis [25].

In addition, in type 2 DM associated with diabetic nephropathy, the hypoglycemic index increases, and at the stage of programmed HD, the state of severe hypoglycemia is associated with a high risk of dementia and ACVA [26]. On the other hand, a high amplitude of daily fluctuations in glycemia more than doubles the probability of stroke due to the development of high-grade ventricular arrhythmias [26].

Y.W. Chu et al. (2017), when evaluating in a population study the association between hypoglycemia and deaths during programmed HD, recorded at least one episode of hypoglycemia during the year before the start of HD in 19.18% of patients, and the complication severity index was associated with more frequent episodes of hypoglycemia. Mortality and hypoglycemia severity after the HD session increased with an increase in the number of previous hypoglycemic episodes. In patients with previous episodes of hypoglycemia, the risk of death was 15% higher than in those who did not have episodes of hypoglycemia, and the risk of subsequent severe hypoglycemia increased by 2.3 times [27].

Thus, glycemic control with the maintenance of the target blood glucose level in patients with end-stage CKD, receiving programmed HD, will prevent the development of ACVA in this cohort of patients.

Chronic heart failure. Uncontrolled HT and anemia represent the leading pathogenetic mechanisms of CHF development in patients with end-stage CKD [28]. An increase in wall thickness and the dilatation of the ventricular cavity of the heart are accompanied by an increase in atrial pressure, which contributes to the development of atrial fibrillation and associated stroke. In addition, in the pre-dialysis stages of CKD in CHF, the renin-angiotensin-aldosterone system is hyperactivated, which leads to sodium and water retention in the kidneys as a result of angiotensin II [29].

It has been revealed that in CHF, oxidative stress develops during programmed HD, which is associated with an increase in the synthesis of active oxygen radicals and a decrease in the level of antioxidants in CKD patients [30]. Some studies have reported that angiotensin II is able to influence brain structures through areas that are not protected by the blood-brain barrier and activate the sympathetic nervous system [31, 32]. The negative effect of angiotensin II on the cardiovascular system also consists in the acceleration of cardiomyocyte apoptosis, proliferation of smooth muscle cells, development of endothelial dysfunction, as well as profibrotic and proarrhythmic effects [29], which is confirmed by the presence of left ventricular hypertrophy in patients at the start of the programmed HD in 42.20% of cases, as well as CHF in 37.61%, and atrial fibrillation in 19.27% of cases [8].

In patients on programmed HD, an increase in the left atrial cavity due to volume overload additionally contributes to the occurrence of stroke. The narrow cone-shaped form and unevenness of the inner surface of the left atrial appendage leads to a high risk of blood clots in patients on programmed HD.

International studies have shown that atrial fibrillation occurs in 20% of CKD patients, and its frequency correlates with the degree of GFR decrease [33]. Such an increase in the frequency of atrial fibrillation may be associated with both improved diagnosis and the presence of risk factors for the development of CHF during programmed HD. According to D.Zimmerman et al. (2012), atrial fibrillation is detected in 20% of patients with end-stage CKD [34].

C.S.Perales et al. (2018) analyzed the clinical and laboratory data of 2,348 patients with end-stage CKD on programmed HD. The estimated sample size was 285 patients. In multivariate analysis, older age and duration of HD were independently associated with the presence of atrial fibrillation [35].

In a cohort study, H.L.Hsieh et al. (2020) retrospectively evaluated the relationship of atrial fibrillation and echocardiographic parameters with the causes of death among 393 HD patients with end-stage CKD. In this study, by the start of the renal replacement therapy, 57 (14.5%) patients already had atrial fibrillation, the mean age was 71 years, and the presence of atrial fibrillation on programmed HD aggravated significantly the patients' survival rate [36].

M.Kamijo et al. described a case of stroke and the successful use of endovascular therapy in patients with atrial fibrillation who underwent programmed HD [37].

Y.L.Ding et al. (2020) reported the occurrence of recurrent stroke in the presence of atrial fibrillation in a 54-year-old female patient receiving HD therapy with the successful use of mechanical thrombectomy from the lumen of the right middle cerebral artery [38].

The results of a prospective cohort population study by M.Wakasugi et al. (2020) involving 247 patients on programmed HD without cardiovascular disease, where 43 patients developed cardiovascular complications over a 4-year period, are noteworthy [39].

The role of circulating ANGPTL-2 (angiopoietin-related protein-2) levels and its relationship with the risk of mortality in patients undergoing programmed HD are currently being discussed [40]. Thus, it was revealed that the ANGPTL-2 level can serve as a marker of premature aging progression and the subsequent risk of mortality in patients with uremia [40]. Previous studies have also demonstrated that ANGPTL-2 levels are usually elevated in stroke, which is associated with severe brain damage [41]. In this regard, according to the researchers, a decrease in the level of ANGPTL-2 may be a useful neuroprotective strategy in stroke [41].

Thus, the treatment of CHF with the prevention of left atrial cavity enlargement and the blood clots appearance, as well as the neuroprotective therapy with a decrease in circulating ANGPTL-2, may become the most important aspect in preventing the development of ACVA in patients receiving programmed HD.

Mineral metabolism disorders. The critical value of the calculated GFR at which disorders in phosphorus-calcium metabolism begin to be recorded is considered as 50 ml/min/1.73 m^2 [1,2]. Mineral bone disorders are widespread among dialysis-dependent patients, occurring in approximately 80% of cases [42]. An increase in the level of blood phosphorus in patients undergoing programmed HD is associated with an increase in the incidence of CHF and mortality [36].

M.Kitamura et al. (2020) analyzed data from patients with end-stage CKD undergoing programmed HD. The results of multiple linear regression analysis showed that a decrease in serum calcium levels is significantly associated with an increase in BP in the group of patients with hemorrhagic stroke [43].

C.Thongprayoon et al. (2020) investigated the relationship between calcium phosphate (CaP) intake and mortality in hospitalized patients [44]. Thus, among the 14,772 patients included in their study, there were 8% of patients with stroke, 9% of patients with CHF, 21% of patients with ischemic heart disease, and 24% of patients with DM. The highest mortality risk was recorded in hospitalized patients with CaP values of 45 mg^2/dL^2 or higher in both CKD and non-CKD patients. As noted by the researchers, high CaP levels on admission were independently associated with an increased risk of in-hospital mortality, and a CaP value of 45 mg^2/dL^2 or higher was associated with the highest risk of in-hospital mortality in both CKD and non-CKD patients. In the subgroup of patients with CaP levels of 45 mg^2/dL^2 or higher, GFR was significantly lower, and serum phosphorus was higher [44].

The pathogenetic mechanism of the occurrence of mineral and bone disorders includes vitamin D deficiency, decreased calcium absorption from the gastrointestinal tract, increased phosphorus blood level, alteration in the functions of the calcium-sensitive and vitamin D receptors of the parathyroid glands, increased synthesis of parathyroid hormone, increased levels of fibroblast growth factor-23, and vascular and soft tissue calcification [45].

Fibroblast growth factor-23 is synthesized by osteocytes in response to an increase in the blood phosphorus level. Serum phosphorus concentrations at the initial stages of CKD due to a compensatory increase in the level of fibroblast growth

factor-23 remain within the normal range for a long time, leading to hyperphosphatemia only at the onset of the pre-dialysis stage of CKD [45], which stimulates the hypersecretion of fibroblast growth factor-23 and parathyroid hormone, and the proliferation of the parathyroid glands [44,45], ultimately leading to the development of resistance of the bone skeleton to parathyroid hormone [44].

Vascular calcification as an outcome of impaired mineral metabolism is closely associated with increased bone resorption and adynamic bone remodeling, but often precedes bone changes [44]. An increase in the concentration of fibroblast growth factor-23 is an independent predictor of mitral valve calcification and thickening of the carotid intima-media complex in CKD patients [46].

According to K.L. Nowak et al., patients with end-stage CKD who undergo programmed HD have increased levels of parathyroid hormones and vitamin D deficiency [42].

X. You et al. assessed the effect of parathyroid hormone and vitamin D supplementation on stroke risk in a cohort study of 980 patients on ambulatory peritoneal dialysis [47]. The primary endpoint was defined as the first episode of stroke, and the combined endpoint included death or transfer to HD during follow-up. The final analysis included 757 patients, where the mean follow-up period was 54.7 months. The median stroke rate among the study participants was 18.9 (interquartile range 15.7–22.1) per 1000 person-years. A significant nonlinear correlation was also found between baseline intact parathyroid hormone levels and the risk of stroke; and vitamin D supplementation reduced the risk of ACVA in patients on ambulatory peritoneal dialysis [47].

In their study, A. Talebi et al. (2020) showed significantly high levels of uric acid and low levels of vitamin D in blood among patients with ischemic stroke. Phosphorus level was not a significant predictor of ischemic stroke [48]. The authors explained these data by the fact that the study involved patients without severe renal dysfunction. Meanwhile, back in 2007, a group of researchers led by R. Dhingra published the results of a prospective follow-up of the Framingham Offspring Study, which showed an increase in the risk of cardiovascular events (including stroke) by 1.31 times (95% confidence interval; 1.05–1.63) with a 1 mg/dL increase in phosphorus level [49].

In the publication by H. Onder and G. Arslan (2020), the potential role of parathyroid hormone in the development of subclinical and clinical vascular diseases of the brain was noted [50]. The clinical and demographic data of 158 patients with ischemic stroke were retrospectively assessed using a computerized system. In 31 (19.6%) patients, an increased level of parathyroid hormone was shown. Moreover, a high level of this hormone was significantly more often noted in stroke associated with extracranial atherosclerosis. Notably, logistic regression analysis also confirmed that high parathyroid hormone levels represent a significant variable in determining stroke associated with an extracranial subtype of atherosclerosis ($p = 0.024$).

Y. Takashi et al. (2020) analyzed the parameters of bone mineral disorders in 119 patients with infection, systemic inflammation, atherosclerosis, and cardiac events who underwent programmed HD. The level of fibroblast growth factor-23 in blood serum was independently associated with the concentration of calcium ($\beta = 0.276$; $p < 0.001$) and phosphorus ($\beta = 0.689$; $p < 0.001$) in the blood serum [51]. However, the level of fibroblast growth factor-23 in the blood was not associated with the parameters of cardiac dysfunction, atherosclerosis, infection, or systemic inflammation [51].

Thus, patients with end-stage CKD undergoing programmed HD need to control the phosphorus-calcium metabolism in order to prevent the development of strokes and extraosseous calcification, in particular of cerebral vessels.

Conclusion. Recently, there has been an active discussion about cardiovascular events and stroke in patients with end-stage CKD who are undergoing programmed HD. The study of stroke risk factors in patients with end-stage CKD requires further development. The timely diagnosis of cardiovascular diseases and the secondary prevention of ACVA, including adequate antihypertensive and hypoglycemic therapy, as well as the correction of heart failure using renin-angiotensin-aldosterone system blockers and the elimination of bone mineral disorders remain to date a highly sought approach in the improvement of the quality of life and survival rate indices of this category of patients.

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