GENERAL REVIEW

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Risk factors for cardiovascular disease in children on chronic hemodialysis – Uremia-related (non-traditional) risk factors, part II

Faktori rizika od nastanka kardiovaskularnih bolesti kod dece na hroničnoj hemodijalizi – Uremijski (netradicionalni) faktori rizika, deo II

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Introduction

As among adults with chronic kidney disease, cardiovascular disease has recently emerged as a significant source of morbidity and mortality even among children with chronic kidney disease. Both traditional and non-traditional cardiovascular risk factors are present among children with chronic kidney disease, and many of these risk factors are closely intertwined with the development and progression of chronic kidney disease. Although few pediatric data are available, management of children with chronic kidney disease, as well as management of adults, should probably include treatment of these risk factors to avoid the development of early cardiovascular disease. In addition to the traditional risk factors, there are a lot of non-traditional or uremia-related risk factors. Non-traditional risk factors are marked as uremic toxins and sometimes it is difficult to separate them from the metabolic disturbances induced by chronic renal failure.

Anemia

Anemia is the second most common non-traditional risk factor for cardiovascular disease (CVD) in children and adolescents with chronic kidney disease (CKD). Unlike the other uremic risk factors, anemia occurs relatively early in CKD due to chronic renal failure [1, 2]. The etiology of anemia is multifactorial: shortened lifespan of erythrocytes, chronic blood loss and inadequate erythropoiesis. It was found that erythrocytes in dialysis patients are sensitive to mechanical, osmotic and oxidative factors; therefore the reason for shortening of the lifespan of red cells should be sought in the corpuscular factors. Also, these patients are prone to chronic blood loss, usually during the act of dialysis; and also because of occult bleeding from the gastrointestinal (GI) tract, as well as due to taking of blood for various laboratory analyses. The most important cause of anemia in patients with CKD is the lack of erythropoietin (EPO). Also the following contributes to the onset of anemia: decreased resorption of iron from the GI tract, lack or loss of folate and vitamin B12, as well as the development of fibrosis of the bone marrow due to the secondary hyperparathyroidism which compromises erythropoiesis [3].

Despite of the widespread use of recombinant erythropoietin as a stimulating agent, recent data from the Chronic Kidney Disease in Children (CkiD) Study [2] show that when the glomerular filtration is reduced below the value of 43 mL/min/1.73 m^2, every subsequent drop of 5 mL/min/1.73 m^2 leads to a decrease in the concentration of hemoglobin by 0.3 g/dL [2].

According to the CKiD study [2], the prevalence of anemia in CKD patients (stages 2–4) is 38–48%, and in patients on HD 40–67% (Table 1). Until recently, the occurrence of anemia after kidney transplant was not given great importance; however, recent studies have shown that due to immunosuppressive therapy administered after the transplantation, the prevalence of anemia is in the range 61–86% [4].

Malnutrition and inflammation

As of recently, oxidative stress, chronic inflammation and malnutrition are defined as new risk factors in adult patients on hemodialysis HD. High levels of the same

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Table 1

Nontraditional risk factors for the cardiovascular disease (CVD) in children with chronic kidney disease (CKD)

Uremic patients risk factors	CKD (%)	HD (%)	Transplant (%)
Anemia	38–48	40–67	32–64
Raised Ca × P	30–40	53–85	
Hyperparathyroidism	30–45	50–60	
C-reactive protein		76	16
Hyperhomocysteinemia		87–92	25–98
Hyperalbuminemia		76	16

Data from the Chronic Kidney Disease in Children (CkiD) study [2]; HD – hemodialysis.

inflammatory markers have been identified in children undergoing treatment with hemodialysis (HD) [5, 6]. There is strong evidence that confirms that inflammation is a leading risk factor for CKD in children, although Goldstein et al. [7] showed a reduction of proinflammatory cytokines in children with end stage renal insufficiency, whose therapy also contains aspirin. The quality of water for dialysis, biocompatibility of the dialysis membrane and the vascular access are the key factors that can trigger the inflammatory cascade and which are maintaining the low grade chronic microinflammation. Panichi et al. [8] have discovered that C-reactive protein (CRP) levels are high in 25% of pediatric patients with CKD and in 50% of patients on HD. Patients on HD, whose concentration of CRP is > 15.8 mg/L have a 2.4 times bigger risk of a cardiovascular death compared to patients whose CRP is < 3.3 mg/L. Malnutrition is an important problem in children with terminal renal insufficiency. Hypoalbuminemia is an important marker of malnutrition. Failure to correct the hypoalbuminemia through the diet, suggests that other factors are responsible for the reduced concentration of albumin in these patients. It is certain that systemic inflammation is associated with malnutrition. Moreover, the increased CRP along with the decreased levels of albumin has been recognized as a powerful predictor of mortality in patients on dialysis. A significant inverse correlation between the proteins of the acute phase of inflammation (CRP and ferritin) and markers of malnutrition (albumin) has been shown. Thus, inflammation is closely associated with malnutrition in children with terminal renal failure. In patients on hemodialysis, malnutrition occurs due to the loss of appetite, lack of nutrition, increased loss of nutrients during the HD, the presence of uremic toxins, increased metabolism, the presence of comorbidities (diabetes mellitus, infection, sepsis, congestive heart failure), increase of oxidative stress and the use of a biocompatible dialysis membrane [9–11].

Natriuretic peptides

Natriuretic peptides are a well-described family of hormones, which play the main role in the homeostasis of salt and body volume. The synthesis and release of these natriuretic peptides are generally stimulated by an increase of the extracellular fluid volume, which is observed through the atrial and ventricular stretch receptors. Their main role is to induce the natriuresis by effecting the renal hemodynamics and tubular function. This role of induction of the natriuresisis is limited in patients with CKD and end stage renal disease (ESRD). Brain-type natriuretic peptide (BNP) and N-terminal (NT)-proBNP are predominantly excreted in the kidneys and have a significant potential for clinical use in this population [9, 10].

There is a small number of publications on the values of natriuretic peptide in children with CKD. Rinat et al. [12] followed the BNP and NT-proBNP in 75 children with CKD (24 of which were treated with HD) and correlation with echocardiographic parameters. In their conclusion, they have published that the levels of BNP and NT-proBNP are significantly elevated in patients with terminal renal failure who are treated with HD. It was even observed that the value of BNP and NT-proBNP is increased in asymptomatic patients in the early stages of CKD. Despite the fact that the levels of these peptides are strongly dependent on the glomerular filtration rate, hemoglobin levels, left ventricular hypertrophy, diastolic dysfunction and diastolic blood pressure, the authors believe that monitoring of natriuretic peptides can help in the assessment of asymptomatic cardiac damage in children with CKD [9, 10].

Homocysteine

Mild to moderate hyperhomocysteinemia is observed in approximately 60–70% of patients with CKD and in more than 90% of patients treated regularly with hemodialysis [2]. Renal function is an important determinant of the concentration of homocysteine in the plasma, therefore through all stages of CKD, between the levels of homocysteine and glomerular filtration, an inverse relation is maintained which is independent from the primary renal disease. The etiology of hyperhomocysteinemia in CKD is unclear. Since there is no significant renal excretion of homocysteine, it is considered that the cause of hyperhomocysteinemia is the deterioration extrarenal metabolism of homocysteine [13]. It is considered that hyperhomocysteinemia occurs as a consequence of the reduced activity of key enzymes involved in the metabolism of homocysteine (methionine synthase, N5, N10-methyl tetrahydrofolate reductase, cistation β-synthase and betaine-homocysteine methyltransferase). Hyperhomocysteinemia blocks the degradation of asymmetric dimethylarginine (ADMA), it also contributes to the accumulation of ADMA in the endothelium of blood vessels and it activates the onset of atherosclerosis. According to the results of observational studies conducted in this group of patients, the high level of homocysteine is a risk factor for the cardiovascular mortality and vascular disease. Pathological mechanisms by which hyperhomocysteinemia promotes atherosclerosis are still unclear. Experimental evidence supports a number of options, including the damage to endothelial cells, increased oxidation of LDL, increased platelet aggregation mediated by thromboxane, inhibition of protein C anticoagulant and stimulated smooth muscle cell proliferation. In this way, hyperhomocysteinemia potentiates the endothelial dysfunction and oxidative stress, it manifests the prothrombotic effects and impairs the coagulation status. Although it is proven that the therapeutic use of folic acid and the vitamin B reduce plasma homocysteine levels in this population, so far it is unknown whether it also reduces the mortality [9].

Asymmetric dimethylarginine

A high concentration of asymmetric dimethylarginine (ADMA) is a risk factor for the onset of cardiovascular complications in children on hemodialysis. High concentrations of ADMA (> 2.22/mol/L) are caused by the reduced activity of the enzyme of dimethylarginine dimethylaminohydrolase (DDAH). Microinflammation, diabetes mellitus, hyperhomocysteinemia and oxidative stress significantly reduce the activity of this enzyme and increase the concentration of ADMA. ADMA blocks the production of nitrogen oxide (NO) in the endothelial cells and contributes to the onset of the atherosclerosis. The absence of biologically active NO is associated with leukocyte-platelet aggregate adhesion. These mechanisms contribute to the onset of acute atherothrombotic events which increases the rate of cardiovascular mortality [13, 9].

Oxidative stress and adiponectin

Increase of oxidative stress is a risk factor for the onset of atherosclerotic cardiovascular complications in patients on hemodialysis. Oxidative stress and elevated concentrations of oxy-LDL block the activity of DDAH and reduce the degradation of ADMA. As it was said before, accumulation of ADMA disrupts functioning of the L-arginine/NO system in endothelial cells, which leads to the reduced levels of NO and the development of atherosclerosis. The use of L-arginine, vitamin E and N-acetylcysteine significantly reduces the level of oxidative stress and it reduces the risk of cardiovascular complications in patients on HD [11, 14].

Adiponectin is a product of the fat tissue which is involved in the lipid metabolism and the regulation of the glucose metabolism. Low levels of adiponectin are associated with the known cardiovascular (CV) risk factors such as dyslipidemia, insulin resistance and chronic inflammation. Some studies suggest that the elevated levels of adiponectin have a protective effect on the onset of CVD [15, 16]. Several studies on children and adults also show a link between the low levels of adiponectin, hypertension and left ventricular hypertrophy (LVH) [16, 17]. In chronic kidney disease, however, despite the increased risk for CVD, the levels of adiponectin were actually higher than physiological. The manner in which this increased level of circulating adiponectin is correlated (interacts) with the cardiovascular risk factors is not clear. Published studies estimate that the relationship between adiponectin and CV risk factors in patients with CKD show inconsistent and sometimes contradictory results. The aforementioned CKiD study [16] monitored the levels of adiponectin in serum as well as the relationship of adiponectin and other anti-inflammatory cytokines which are involved in the regulation of the lipid and glucose metabolism. This is the first study that by the use of the high resolution (HR) gel filtration test, recently discovered, allowing us to analyze the adiponectin in the form of all three complexes. The study shows that the high molecular weight (HMW) complex accounts for about half of the total adiponectin. These studies, along with the studies on adult patients confirm that serum levels of total adiponectin are increased in children with mild to moderate CKD, compared with previously published normal values in healthy children, and it is inversely correlated with the renal function. This increase is accompanied by the elevation of HMW and reduction of the high molecular weight (LMW) complex in the circulation, while the trimmer part remained unchanged. Adiponectin can also be found in urine and its levels are inversely related to the glomerular filtration rate (GFR). The mechanism of these changes in fractions of adiponectin could be caused by the relatively low clearance for HMW oligomers compared to the LMW form. Recent animal studies featuring the fluorescently-labeled recombinant adiponectin indicate that adiponectin is primarily metabolized in the liver, but also through the kidneys. What is the role of the liver in comparison to the kidney in the detection of adiponectin complexes in patients with reduced renal function is not known. The fact remains that the level of adiponectin is significantly decreased after kidney transplantation [15].

Disorders of calcium and phosphorus metabolism and hyperparathyroidism

Disorder of calcium (Ca) and phosphorus (P) metabolism is specific for patients at chronic hemodialysis and presents the most important cause for the onset of the cardiac and vascular diseases in their case. Hyperparathyroidism affects 30–45% of children with CKD in phases 2–4 and almost 60% of children on hemodialysis [18–20]. Among the Turkish children with chronic renal insufficiency, almost 30% have increased levels of calcium-phosphorus products, while 40% of them have the increased levels of the parathyroid hormone [18]. The relationship between the disturbances of the mineral metabolism and the structural vascular changes in children with CKD has been confirmed, and documented in many papers [2, 15, 19]. Although administration of vitamin D supplements in terminal renal insufficiency is the basic therapy for the control of secondary hyperparathyroidism, there is evidence that vitamin D has a direct effect on the deposition of calcium in vascular smooth muscle cells [20, 21].

Structural and functional changes in the left ventricle

Long-term maintenance of the increased pressure and fluid, combined with other risk factors (anemia and hyperparathyroidism) in children on HD may lead to structural changes in the myocardium, such as accumulation of collagen, fibrosis and calcification [22].

Myocardial fibrosis leads to the decreased compliance of the left ventricle. The pathogenesis of myocardial fibrosis includes: angiotensin II, chronically increased parathyroid hormone, increased sympathetic activity, disturbance of the metabolism of phosphorus, a high level of Ca × P product, chronic inflammation, anemia, and other CV risk factors [15, 5].

In children at the stage 2–4 of CKD, the prevalence of LVH is 20–30%, while in patients on HD, the prevalence is 60–85%. Data of the European Dialysis and Transplant Association (ERA-EDTA) [23] shows that in 29% of children on peritoneal dialysis and in 59% of children on hemodialysis has LVH that is proven by echocardiography. In our study the LVH was 60% [24]. Children on HD usually have the eccentric (asymmetric) form of left ventricular hypertrophy and the normal relation between left ventricular mass/left ventricular volume (LVM / LVV) [25, 26].

Unlike adults with CKD, whose early heart failure is associated with systolic dysfunction, in children the systolic function is usually preserved longer, which we have confirmed in our results [26].

In children on HD the diastolic dysfunction precedes the systolic cardiac dysfunction. The prevalence of the diastolic dysfunction is increased in patients who are on chronic HD [2, 22]. One of the reasons for the increased prevalence is the emergence of new Doppler techniques, which allow detection of the diastolic dysfunction at an early stage. Tissue Doppler (TDI) in combination with a conventional (PW) Doppler can provide the additional information about the pressure of left ventricular filling (E/Em) in children on HD, which can facilitate risk stratification and making of the diagnosis [22, 27, 28].

Conclusion

Early recognition of risk factors and treatment of patients with asymptomatic cardiovascular changes is the key for the reduction of the mortality and morbidity in dialysis patients with the developed cardiovascular disease during childhood. By influencing risk factors, including aggressive monitoring and control of blood pressure, dyslipidemia, metabolism of Ca and P, anemia, malnutrition, chronic inflammation and other, it is possible to significantly postpone and improve the cardiovascular outcome of these patients.

Individual assessment of the condition of the cardiovascular system in hemodialysis patients can significantly postpone and improve the cardiovascular outcome and bring about the improvement of the living condition of each patient individually.

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