VITAMIN D NEPHROPROTECTIVE STRATEGY OF CHILDREN WITH CHRONIC RENAL DISEASE

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Abstract. *According to current conception, the process of forming of nephrosclerosis despite the origins is detected by the force of the same cellular and molecular mechanisms. Hence primary triggers cause elevated production of range of cellular response mediators, cytokines and growth factors such as transforming plateled-derived growth factor, fibroblast growth factor, interferon gamma, nuclear factor and others, by means of sequential processes, is followed by the replacement of kidney tissue. One of the most studied aspects of the process of nephrosclerosis is the influence of anginotensin II. Therefore, despite the triggering factors, development and progression of nephrosclerosis all children with chronic renal disease are in a risk group with predisposition for renal insufficiency and it is required to prescribe nephroprotective therapy, i.e. the drugs that will influence one of the links of the nephrosclerosis, in order to slow down its progression. Currently, with nephroprotective goal in early age are used the following elements — angiotensin converting enzyme inhibitors and angiotensin receptors, antogonists (blockers).*

Keywords: *vitamin D; in children nephrosclerosis; nephrosclerosis and vitamin D; the role of vitamin D in the nephrosclerosis; renal protection the protection of children; renal protection strategy in children*

The development of chronic renal failure (CRF) in children is the outcome of most congenital malformations and hereditary diseases of the urinary system, therefore, prevention of the onset and slowing down of its development can be attributed to the predominant development of pediatric nephrology.

According to modern concepts, the process of formation of nephrosclerosis, regardless of the cause of its occurrence, is determined by the action of the same cellular and molecular mechanisms. Thus, primary triggers cause increased production of a number of cellular response mediators, cytokines and growth factors, such as transforming growth factor (TGF-pi), platelet-derived growth factor (PDGF), fibroblast growth factor (TCP), IL-6, interferon-gamma (INF-gamma), nuclear factor kB (NF-kB), etc., which through successive processes lead to the replacement of renal tissue with connective tissue. One of the most studied links in the process of nephrosclerosis is currently the influence of angiotensin II (Ang II).

Angiotensin II, the main effector of the renin-angiotensin system (RAS), is produced systemically and locally in various tissues, including the kidneys, heart, and blood vessel walls. At the same time, all RAS components are present in the kidneys, including angiotensinogen (Ang II substrate) and enzymes involved in the synthesis and breakdown of angiotensin, as well as angiotensin receptors. The intrarenal concentration of Ang II is thousands of times greater than the level of circulating Ang II. Ang II exerts its action through the AT1 and AT2 receptors. Activation of AT1 receptors leads to vasoconstriction, growth stimulation and activation of fibroblasts and myocytes. Through AT2 receptors, Ang II causes vasodilation and an antiproliferative response, as well as an increase in apoptosis activity.

It is known that intrarenal production of Ang II increases in kidney diseases and chronic renal failure. To date, it has also been established that, along with the long-

known effect of Ang II on renal hemodynamics, it also induces other effects directly related to the formation of nephrosclerosis.

The nuclear transcription factor kB (NF-kB), which regulates the transcription of numerous genes in many tissues, including the kidneys, plays a central role in increased intrarenal production of Ang II and in its fibrosing effects. NF-kB is localized in the cell cytoplasm, where it is contained in an inactive form (1 kV). It is suggested that NF-kB activation is a causal factor in actin expression by alpha-smooth muscle cells during the development of renal fibrosis. It has been shown that NF-kB activation stimulates the angiotensinogen gene, thereby providing the production of the Ang II substrate. On the other hand, Ang II formed in the liver and kidneys itself activates NF-kB, which, in turn, in accordance with the mechanism just mentioned, supports the further production of Ang II. Thus, there is an autosecretory vicious circle that provides increased production of Ang II. In addition to Ang II, NF-kB is also activated by tumor necrosis factor-α (TNF-α), whose production, on the other hand, is also induced by NF-kB. This means that a second vicious circle exists: NF-kB induces the production of TNF-α, which in turn activates NF-kB.

Along with Ang II, other vasoactive compounds (endothelin-1, thromboxane A2, prostaglandins) are also activated in the advanced stage of chronic kidney disease. In recent years, the attention of researchers has been drawn to endothelin-1 and nitric oxide (NO). It has been shown that endothelin-1 leads to a pronounced vasoconstriction of the renal vessels, contributing to a decrease in renal blood flow and glomerular filtration rate and leading to ischemic damage to the kidneys. In addition, it is currently considered as a growth factor that enhances the production of the matrix by mesangial cells, epithelium and fibroblasts, which leads to the development of glomerulosclerosis.

Based on a single, independent of the triggering factor, mechanism of development and progression of nephrosclerosis (described above), all children with chronic kidney disease from the risk group for the development of chronic renal

failure should be given nephroprotective therapy, i.e. drugs that act on certain links of nephrosclerosis, slowing down its progression.

At the present stage, in children with chronic kidney disease, prevention of the development of chronic renal failure is carried out as follows: treatment of the underlying disease (including surgical correction); fight against infection; use of nephroprotective agents.

Currently, angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor antagonists (ARA) are used for nephroprotective purposes in childhood [30-32]. The mechanism of action of all ACE inhibitors is reduced to the blockade of the formation of angiotensin-converting enzyme, which catalyzes the conversion of inactive Ang I into the vasoactive Ang II peptide. Accordingly, the pharmacological blockade of ACE leads to a decrease in the synthesis of Ang II. The mechanism of action of ARA is the blockade of type 1 Ang II receptors, as a result of which the circulating or locally synthesized peptide cannot bind to its receptors and have a pathological effect on tissues.

But the use of ACE inhibitors is limited in stage 3-5 CKD, since these drugs can increase serum creatinine and increase hyperkalemia. Therefore, with severe nephrosclerosis, the appointment of ACE inhibitors is contraindicated, due to the risk of a sharp deterioration in the filtration function of the kidneys.

The second group of drugs used for nephroprotective purposes - ARA - like ACE inhibitors, eliminates the effects of the most dangerous "nephrotoxic" agent - angiotensin-II. To date, 2 multicenter controlled studies have been completed on the use of this group of drugs in patients with type 2 diabetes mellitus with initial CKD: the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) study and the IDNT (Irbesartan Diabetic Nephropathy Trial) study. Both studies convincingly demonstrated a pronounced nephroprotective effect of the AT1 receptor blockers losartan and irbesartan in patients with diabetic nephropathy. Vitamin D plays a dual role in the progression of nephrosclerosis.

Firstly, vitamin D, being a hormone according to the modern concept, is converted into an active form in the kidney tissue by the action of the enzyme 1-alpha-hydroxylase. Accordingly, a decrease in the mass of kidney tissue leads to a decrease in the concentration of the active form of vitamin D.

Secondly, the active form of vitamin D, according to modern literature, affects the links of nephrosclerosis, and also plays an important role in hormonal and metabolic disorders that accompany CRF.

The interaction of vitamin D with TGF-β1 was revealed, with the addition of vitamin D, the expression of alpha-SMA, the formation of type I collagen, and the expression of thrombospadin-I were suppressed. Vitamin D suppresses profibrotic TGF-β1, in tubular epithelial cells.

Another potential mechanism for vitamin D and TGFβ1 antagonism is that vitamin D protects tubular epithelial cells by inhibiting signals from β-catenin, a critical signaling pathway to TGFβ1/integrin-related kinase that transduces EMT signals. Inhibition of tubulointerstitial fibrosis by vitamin D has been confirmed in an animal model with unilateral ureteral obstruction. When paricalcitol was injected into mice for 7 days, the severity of tubulo-interstitial fibrosis (TIF) was less than in the control, the expression of α-SMA, fibronectin, and collagen was significantly reduced, and the expression of E-cadherin and D receptors was largely restored.

Conclusion. As a result of creating a biopathological model of nephrosclerosis in animals, the mechanisms of sclerotic changes in the kidneys were discovered. The use of vitamin D in such animals had a nephroprotective effect due to the anti-inflammatory effect, inhibition of the proliferation of mesangial cells and podocytes, a decrease in RAS activity, prevention of glomerular hypertrophy, a decrease in proteinuria, the production of fibrogenic cytokines, and inhibition of EMT. Due to this action of vitamin D, the progression of glomerular and tubulointerstitial fibrosis is slowed down and the progression of chronic renal failure is inhibited.

BIBLIOGRAPHY

1. Warady B.A., Chadha V. Chronic kidney disease in children: the global perspective. Pediatr. Nephrol. 2007; 22(12): 1999-2009.

2. Kidney Disease: Improving Global 0utcomes (KDIG0) CKD Work Group. KDIG0 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney International. 2013; Suppl. 3: 1-150.

3. Zaritsky J.J., Warady B.A. Chronic kidney disease in the neonate. Clin. Perinatol. 2014; 41(3): 503-15.

4. Schlondorff D.O. Overview of factors contributing to the pathophysiology of progressive renal disease. Kidney. Int. 2008; 74(7): 860-6.

5. Jefferson J.A., Shankland S.J. The pathogenesis of focal segmental glomerulosclerosis. Adv chron. Kidney. dis. 2014; 21(5): 408-16.

6. Yang H.C., Fogo A.B. Mechanisms of disease reversal in focal and segmental glomerulosclerosis. Adv. chron. Kidney. dis. 2014; 21(5): 442-7.

7. Khan Z., Pandey M. Role of kidney biomarkers of chronic kidney disease: An update. saudi. J. Biol. Sci. 2014; 21(4): 294-9.