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## Kidneys and autonomic dysfunction in children and adolescents (part I)

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**Abstract.** *The article discusses the mechanisms of interaction, development and progress of cardiovascular complications in children and adolescents with chronic kidney disease. The dominant role of autonomic dysfunction in the development of cardiovascular disorders is emphasized. The mechanisms are described by which an increase in the activity of sympathetic part of autonomic nervous system leads to kidney damage. Interaction of sympathetic nervous system and renin-angiotensin system during the formation of cardiovascular and kidney diseases is considered as a component of adaptive process of the body. The universal pathogenetic factor that accompanies the development of autonomic dysfunction and chronic kidney disease in children and adolescents is activation of renin-angiotensin system. The general mechanisms for the development of cardiorenal disorders determine further unidirectional approaches to the diagnosis and treatment.*

**Keywords:** *children; chronic kidney disease; autonomic dysfunction; arterial hypertension*

### Introduction

Modern medicine pays much attention to comorbid pathology, in particular the kidney and heart diseases combination with mutually shared risk factors [1, 2]. Heart and kidney comorbid state whereby acute or chronic dysfunction in one organ induces acute or chronic dysfunction of the other is now defined as a cardiorenal syndrome [1, 3–5]. Cardiorenal interactions are common in patients with chronic kidney disease (CKD) (cardiorenal syndrome type 4) [1, 4], but unfortunately, little attention has been so far paid to this issue in pediatrics [5].

Children with CKD have been found to have high cardiovascular risks that significantly exceed those among their healthy peers [6, 7], and in the terminal stage of CKD, cardiovascular mortality rates are 30 times higher than in the age-matched general pediatric population [8].

Although the causal and risk factors for cardiovascular disease in CKD have not been fully identified, they are usually classified as traditional and non-traditional ones. The traditional factors include, first of all, sympathetic hyperactivation, hypertension, hyper- and dyslipidemia, abnormal calcium-phosphorous metabolism, etc. Non-traditional risk factors are commonly consi-

dered as factors associated with uremia in the CKD population [6, 9].

The Chronic Kidney Disease in Children (CKiD) observational cohort study of 586 children aged 1–16 years with stage 2–4 CKD found that 39 % of patients had at least one risk factor, 22 % had two risk factors and 13 % had three cardiovascular risk factors [10]. The number of these risk factors increases as CKD progresses and is the greatest in children with end-stage CKD [6].

As CKD progresses, cardiac function decrease occurs owing to arterial hypertension (AH), ventricular hypertrophy, and diastolic dysfunction development which are associated with an increased risk of adverse cardiovascular events [1, 2, 11].

### Autonomic disorders in children and adolescents with CKD

Recently, data on the role of the sympathetic nervous system (SNS) in the development of comorbid renal and cardiac dysfunction, particularly in adult patients with CKD, have been accumulated in the literature, but it has not been studied in detail among the pediatric population with CKD [12]. The mechanisms for humoral parameters interaction

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and their effect on such an important endogenous system as the renin-angiotensin-aldosterone system (RAAS) have not been well studied in children [13]. The results of a recent study on the autonomic nervous system (ANS) in children with CKD have shown the development of adverse cardiovascular effects similar to those previously encountered in adult patients. This demonstrates an important role of ANS dysfunction and SNS over-activity in the development of hypertension associated with CKD and adverse cardiovascular effects in adults as well as emphasizes its childhood origin [12]. A broad view of the humoral mechanisms existing in the pediatric RAAS might contribute to a more effective and rational pharmacotherapy in children [13].

Given the link between both the SNS over-activity and ANS dysfunction and the resultant increased risk for both cardiovascular diseases and CKD progression, a strategy developed to decrease SNS over-activity is essential in the management of pediatric CKD [12].

There are well ascertained pathophysiological links between pediatric hypertension and CKD. Some types of CKD can result in hypertension, which in turn can lead to CKD in adults [14].

According to previous studies, an extremely high prevalence of subclinical cardiovascular diseases has been confirmed in children with early stages of CKD [7, 8]. In the examination of children with I–III stage CKD, we observed elevated blood pressure (BP) in 22.3 % of patients, hypertension in 34.1 % of patients, while the highest rates were among patients with stage III CKD (58.8 %) [15]. Other researchers found that 63 % of children with I–IV stage CKD had abnormal BP [8].

According to epidemiological data, every second child or adolescent has CKD with AH [16]. Among children and adolescents with end-stage renal failure, 48 to 79 % are hypertensive, including 20 to 70 % of individuals having uncontrolled AH [17, 18]. A recent study has shown that children with uncontrolled AH have a higher risk of CKD progression than children with normal BP or controlled AH [19].

A high sympathetic nerve activity at the late stage of kidney disease greatly exceeds that in essential hypertension and is equal to or higher than that observed in heart failure [20].

## Autonomic dysfunction in children and adolescents

The pathogenesis of autonomic dysfunction (AD) is based on the imbalance between the sympathetic and parasympathetic systems due to the disintegration of higher autonomic centers [21–24]. Structural and functional changes in the area of suprasegmental structures lead to a generation of pathologically intensified excitation resulting in the chronicity of autonomic disorders, maintaining the predominance of one ANS division activity over the other (sympathetic or parasympathetic) [21]. If the generator of pathologically intensified excitation is localized mainly in the posterior hypothalamus, then sympathicotonia is observed in children, if in the anterior hypothalamus — vagotonia.

An essential role of the ANS is ensuring two key global functions: to maintain homeostasis (the internal steady state within an organism) and the autonomic maintenance

of the activity (mobilization of body functional systems in response to external factors for an adaptation to changing environmental conditions) [21].

On the one hand, 25–80 % of all chronic diseases are accompanied by autonomic disorders [23, 24]. On the other hand, AD originated in childhood or adolescence becomes an adverse condition and a predictor of many diseases. Thus, there are almost no pathological conditions independent of the ANS disorders in which they are found.

AD as a separate disease is mainly diagnosed in childhood [26]. The incidence and prevalence of AD in children and adolescents is significant accounting for 50–75 % of cases in patients with non-communicable pathology [27]. Unlike adults, children appear predisposed to greater changes in the autonomic imbalance, while at the same time, a life-threatening organic pathology is more difficult to suspect in children [22].

One of the main features of ANS imbalance relates to the first symptoms of AD occurrence even in the neonatal period reaching maximum manifestations in adolescence [24–26]. Regarding the development of AD in adolescents, the neuroendocrine remodeling that is actively occurring during puberty would also need to be borne in mind. Therefore, unstable autonomic regulation is observed in 95 % of adolescents [23].

AD results from a combined influence of several etiological factors, among which there are two main groups: congenital and acquired [28]. The causes of autonomic imbalance are hereditary predisposition, pathology of the perinatal period, consequences of traumatic brain injuries and neuroinfections, chronic inflamed lesion foci and somatic diseases, extreme physical activity, emotional disturbances, hostile environments, etc. [9, 10, 23, 28].

SNS overall function is that of performing the body adaptation responses when faced with changes in the external and internal environment, enhancing ergotropic regulation by increasing production of stress hormones and activation of catabolic processes, while the parasympathetic system is the main controller of the internal environment (homeostasis) owing to trophotropic effects [22]. Neudakhin E.V. formulated the interaction between two divisions of the ANS in AD development. This hypothesis stated a compensatory increase in the activity of both sympathetic and parasympathetic ANS divisions with characteristic of intensive adaptation stage at the onset of AD following a causative agent action. Thereafter, if a trigger exists for a long time (a state of chronic stress), the adaptive activity of hormonal mechanisms reinforces and the role of neuromechanisms is relatively reduced (an increase in one of the ANS division activity is accompanied by a compensatory unidirectional but insufficient change in the other division). This is a stage of relative compensation. With further maintaining the increased activity of one division of the ANS, instead of unidirectional changes in the other division, its inverse response occurs (for example, rather than enforcing compensatory activity, its decreases) indicating the decompensated stage at the autonomic level [22].

In many children with AD, an increased blood content of stress hormones is determined, which is associated with an enhancement of the hypothalamic-pituitary system ac-

tivity followed by the sympathoadrenal system mobilization. The sympathoadrenal hyperactivity contributes to a decrease in insulin sensitivity in peripheral tissues resulting in stimulation of insulin production and secretion. Stress hormones act to reduce glucose disposal, stimulate lipolysis, thus contributing to free fatty acids, cholesterol, and other accumulation in the body [22].

AD may manifest itself as an impaired regulation of various organs and systems, but cardiovascular system is typically affected [23, 24, 34]. One of the most common conditions is hypertensive type of dysautonomia (hypersympatheticotonic) that causes AH development. On epidemiological evidence, hypersympatheticotonia is observed in more than 50 % within the general population of AH patients [29].

That is, elevated BP arises from childhood and adolescence. Thus, at present, AH in children and adolescents has graduated from the group of rare pathology to the category of common diseases. AH is a major socio-economic and medical problem while remaining a crucial risk factor

for coronary heart disease and brain diseases with overall mortality rate exceeding 50 % [30]. AH also leads to kidney damage, which is diagnosed in every third adult patient with a more than 10-year history of elevated BP [14].

Among normal-weight children, the prevalence of AH is about 3.5 % [31].

## Pathogenesis of hypersympatheticotonia

Currently, there is overwhelming evidence to support a great importance of SNS chronic activation in both essential and renal hypertension [32]. Undoubtedly, hypersympatheticotonia is the first universal step in cardiovascular and cardiorenal disease continuum.

The mechanism of hypersympatheticotonia is complex and has not been completely studied. There are several ways of hypersympatheticotonia development (Fig. 1).

First of all, it is worth noting the renin-angiotensin-aldosterone system activation. The latter increases renin synthesis in cells of the renal juxtaglomerular apparatus, which

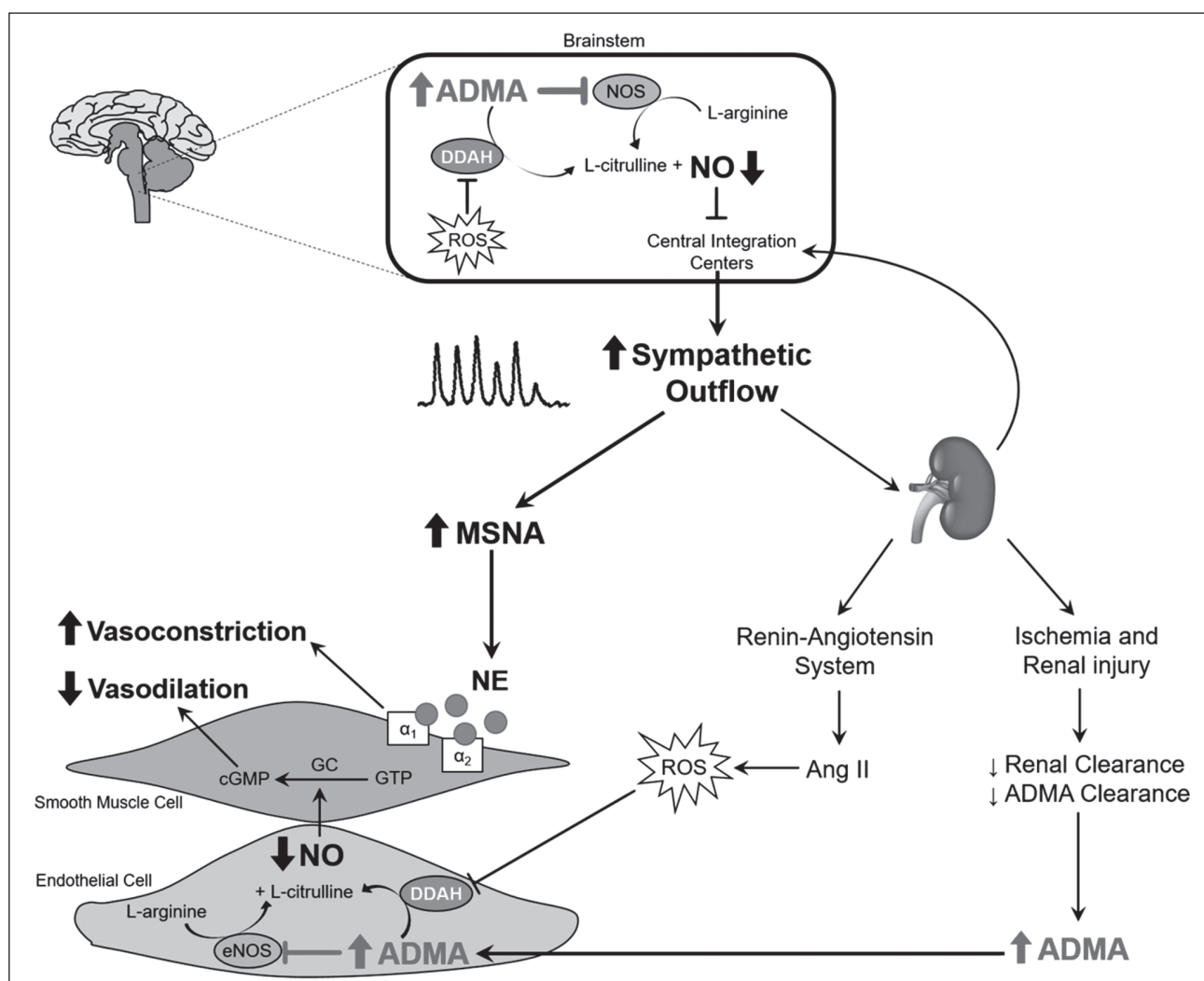


Figure 1. Pathogenesis of hypersympatheticotonia (according to [33])

**Notes:** ADMA — asymmetric dimethylarginine; Ang II — angiotensin II; DDAH — dimethylarginine dimethylaminohydrolase; GC — guanylate cyclase; GTP — guanosine-5'-triphosphate; cGMP — cyclic guanosine monophosphate; NO — nitric oxide; NOS — nitric oxide synthase; eNOS — endothelial nitric oxide synthase; NE — nor-adrenaline; MSNA — muscle sympathetic nerve activity; ROS — reactive oxygen species.

cleaves angiotensinogen to angiotensin I (Ang I) (weak vasoconstrictor), and that, in its turn, is further cleaved into angiotensin II (Ang II) by the action of angiotensin-converting enzyme (ACE). Ang II is a potent vasoconstrictor with numerous peripheral and central actions [33]. It causes direct vasoconstriction of the peripheral vessels and also modulates peripheral SNS by stimulating norepinephrine release from sympathetic nerve terminals. In addition to converting Ang I into Ang II, ACE inactivates bradykinin, integrating RAAS and kallikrein-kinin system [9, 13].

The role of reninase, which is a kidney-derived molecule exerting potent nephro- and cardioprotective effects not related to its enzymatic activity, is controversial in the pathogenesis of AH in CKD patients [9].

In children with both cardiac and renal failure, in general, higher levels of Ang I, Ang II and Ang 1–7 were found than in healthy subjects [13].

However, mechanisms other than RAAS are also involved in sympathetic hyperactivity in CKD and this effect is mediated by sympathetic outflow from the brainstem [33].

Hyperactivity of the sympathetic division of the ANS directly or indirectly via RAAS activation increases the synthesis of endothelin-1 which is a potent vasoconstrictor. This, in its turn, reduces the vascular wall ability to relax in response to vasodilating stimuli and causes systemic microcirculation alteration and impaired perfusion as one of the key non-immune mechanisms of CKD progression. In addition, a local RAAS promoting vasoconstriction has been revealed in the vascular endothelium [34].

## Hypersympathicotonia and endothelial dysfunction

Hypersympathicotonia is associated with a decrease in the production of nitric oxide (NO) as one of the pathogenetic links of endothelial dysfunction (ED) in CKD patients [34, 35]. Reduction in NO bioavailability has been associated with major adverse effect of free radical reactions in oxidative stress in CKD patients [35]. All these factors contribute to the vasomotor type of ED development in patients with CKD. That is, ED manifests itself in an attenuation or absence of endothelial vasodilating reaction and vasoconstriction.

The next mechanism in the development of ED in CKD is a reduced ability of vascular endothelium to synthesize and release NO [36–38]. NO is synthesized from a semi-essential amino acid L-arginine by NO synthase (NOS) and it is of particular importance in a clinical kidney pathophysiology. There is evidence of NO synthesis in endothelial and smooth muscle cells of renal vessels, glomerular mesangial cells and renal tubular cells, so it is an absolutely essential part in the regulation of renal blood flow, kidney excretory function, tubuloglomerular feedback. These effects are partially realized by means of interactions between NO and RAAS, and other bioregulators of renal function.

One of the NO deficiency mechanisms is a reduction in L-arginine availability due to a decrease in its generation in renal tubular cells and impaired transport or cellular uptake as well as depleted arginine pool and increased breakdown of arginine both by arginases and NOS [37]. Low levels of serum arginine and its dimethyl derivatives were found to

be associated with CKD development and/or progression in children [39]. Moreover, the accumulation of glycosylation end-products as CKD progresses may reduce NO effect on its targets [36]. Renal inflammatory process and oxidative stress are responsible for NO inactivation by reactive oxygen species, not only resulting in the loss of endothelial vasorelaxing, antiaggregant and antiadhesive properties of NO, but also mediates the realization of its cytotoxic properties worsening a damage to the renal tissue [40]. Thus, NO actively interacts with other inflammatory mediators and is greatly involved in the tendency of renal inflammatory process. A correlation has been found between the total level of NO production and plasma concentration of asymmetric dimethyl arginine, an endogenous inhibitor of NOS, which prevents the conversion of arginine to citrulline, thus inhibiting NO synthesis [38, 41]. These changes occur from the early stages of CKD in children [42]. Structural changes violating normal renal blood flow are conducive to ischemic changes similar to those that are typical for vasoconstriction in the parenchyma due to increased levels of Ang II, endothelin-1 or reduced NO levels [43].

The literature suggests that ED was observed since stage I CKD in children, the patients demonstrated an increase in plasma concentrations of the most potent endogenous vasoconstrictor endothelin-1, which was accompanied by a decrease in both NO levels and NO/endothelin-1 ratio [34]. Interrelations between biomarkers and ED indicate that CKD patients present with multiple mechanisms of endothelial function disorders [41].

## Aldosterone as an important element and mediator of the RAAS effects

The next component of RAAS is the steroid hormone aldosterone which stimulates renal sodium reabsorption and thereby regulates an extra-cellular fluid volume and potassium metabolism [13, 45]. Aldosterone release from the zona glomerulosa of the adrenal cortex is driven by RAAS activation. In general, its secretion in the body is controlled by RAAS along with potassium ions, atrial natriuretic hormone, adrenocorticotrophic hormone and dopamine. The specific effects of aldosterone are mediated via cell-membrane mineralocorticoid receptors expressed in epithelial cells for sodium transport across the cell membranes (epithelial cells of the distal nephron, distal colon, rectum, salivary and sweat glands) [13, 45].

Aldosterone binds to the mineralocorticoid receptors in the distal tubular epithelial cells of the kidney and promotes sodium ions retention in return of potassium and magnesium ions excretion resulting in fluid retention and electrolyte imbalance. Consequently, it causes a volume-dependent hypertension, cardiac volume overload, hypokalemia and hypomagnesemia [13, 45].

This explains the pathophysiological role of Ang II and aldosterone in the development and progression of cardiovascular diseases.

Besides the classic effects of aldosterone, non-epithelial cells of various organs are also targets for its actions, including the heart and blood vessels. Aldosterone-induced processes of remodeling and enhancement of collagen synthe-



sis in organs and tissues, influence on endothelial function contributing to both renal and cardiovascular diseases progression have been proven [45].

## Increased renal afferent impulses

The kidneys are densely innervated by both renal afferent sensory and efferent sympathetic nerves and interlinked with the CNS via sensory afferent nerves [20, 46]. Increased renal afferent impulses directly influence the sympathetic impulses into the kidney via the efferent nerves that is a decisive factor for synthesis of norepinephrine, a key effector of the SNS [46].

Studies conducted both in animals and among humans have shown that neural signals emanating from the kidneys play a role in enhancing sympathetic impulses in CKD [33, 45]. It seems clear nowadays that the renal sympathetic nerves are central to the pathogenesis of experimental and essential hypertension owing to the effects on renin release, glomerular filtration rate, and sodium reabsorption in the renal tubules [32]. Experimental studies have shown that kidney damage without reduced renal function also leads to increased sympathetic impulses. Furthermore, ligands such as urea and adenosine, which are elevated in CKD, are considered responsible for stimulation of the renal nerves, additionally increasing the sympathetic activation of the ANS [33].

## Outcomes of hypersympathicotonia

Prolonged activation of the SNS causes four types of effects [46]:

1. Hemodynamic effects manifest itself in increased heart rate and vasoconstriction. The hemodynamic effects of the SNS activation in the myocardium are accompanied by an increase in oxygen demand and a decrease in coronary reserve; renal sympathetic stimulation is eventually realized as sodium and water retention.
2. Metabolic effects involve developing insulin resistance, hyperinsulinemia and lipid metabolism disorders.
3. Trophic effects lie in an induction and subsequent stimulation of cardiovascular remodeling as well as ED.
4. Coagulation changes include increased hematocrit, platelet activation, procoagulative action.

## Conclusions

1. The interaction between sympathetic nervous system and renin-angiotensin system in the pathogenesis of cardiovascular and renal disorders is an integral part of the body adaptive adjustment.
2. Activation of the renin-angiotensin system is a universal pathogenic factor that necessarily accompanies the development of autonomic dysfunction and chronic kidney disease in children and adolescents.
3. Common mechanisms for the development of cardiovascular disorders determine convergent approaches to diagnosis and treatment.

**Conflicts of interests.** Author declares the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

## References

1. Raina R, Nair N, Chakraborty R, Nemer L, Dasgupta R, Varian K. An Update on the Pathophysiology and Treatment of Cardiorenal Syndrome. *Cardiol Res.* 2020;11(2):76–88. doi:10.14740/cr955.
2. Ivanov DD, Kuryata OV, Garmysh IP. Renin angiotensin-aldosterone system blockers: chronic kidney disease and cardiovascular risk. *Počki.* 2018;7(2):81–90. doi:10.22141/2307-1257.7.2.2018.127393. (in Russian).
3. Rangaswami J, Bhalla V, Blair JEA, et al. Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies: A Scientific Statement From the American Heart Association. *Circulation.* 2019;139(16):e840–e878. doi:10.1161/CIR.0000000000000664.
4. Ronco C, Bellasi A, Di Lullo L. Cardiorenal Syndrome: An Overview. *Adv Chronic Kidney Dis.* 2018;25(5):382–390. doi:10.1053/j.ackd.2018.08.004.
5. Olowu WA. Epidemiology, pathophysiology, clinical characteristics and management of childhood cardiorenal syndrome. *World J Nephrol.* 2012;1(1):16–24. doi:10.5527/wjn.v1.i1.16.
6. Tian J, Niu L, An X. Cardiovascular risks in chronic kidney disease pediatric patients. *Exp Ther Med.* 2017;14(5):4615–4619. doi:10.3892/etm.2017.5117.
7. Mitsnefes MM. Cardiovascular disease in children with chronic kidney disease. *J Am Soc Nephrol.* 2012;23(4):578–585. doi:10.1681/ASN.2011111115.
8. Hsu CN, Lu PC, Lo MH, Lin IC, Tain YL. The Association between Nitric Oxide Pathway, Blood Pressure Abnormalities, and Cardiovascular Risk Profile in Pediatric Chronic Kidney Disease. *Int J Mol Sci.* 2019;20(21):5301. doi:10.3390/ijms20215301.
9. Skrzypczyk P, Okarska-Napierala M, Stelmaszczyk-Emmel A, Górka E, Pańczyk-Tomaszewska M. Renalase in children with chronic kidney disease. *Biomarkers.* 2019;24(7):638–644. doi:10.1080/1354750X.2019.1642957.
10. Wilson AC, Schneider MF, Cox C, et al. Prevalence and correlates of multiple cardiovascular risk factors in children with chronic kidney disease. *Clin J Am Soc Nephrol.* 2011;6(12):2759–2765. doi:10.2215/CJN.03010311.
11. Vidi SR. Role of hypertension in progression of chronic kidney disease in children. *Curr Opin Pediatr.* 2018;30(2):247–251. doi:10.1097/MOP.0000000000000595.
12. Barletta GM, Flynn J, Mitsnefes M, et al. Heart rate and blood pressure variability in children with chronic kidney disease: a report from the CKiD study. *Pediatr Nephrol.* 2014;29(6):1059–1065. doi:10.1007/s00467-013-2737-8.
13. Suessenbach FK, Burckhardt BB. Levels of angiotensin peptides in healthy and cardiovascular/renal-diseased paediatric population—an investigative review. *Heart Fail Rev.* 2019;24(5):709–723. doi:10.1007/s10741-019-09797-y.
14. Ivanov DD. Nephrology under the microscope: interdisciplinary aspects. *Kidneys and arterial hypertension.* *UMJ.* 2019;132:32–33. (in Ukrainian).
15. Vakulenko LI. 24-hour blood pressure profile in children with chronic pyelonephritis and chronic kidney disease stages I–III. *Počki.* 2019;8(3):139–145. doi:10.22141/2307-1257.8.3.2019.176451.
16. Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. *Pediatrics.* 2017;140(3):e20171904. doi:10.1542/peds.2017-1904.
17. Wühl E, Schaefer F. Treatment of Hypertension in Chronic Kidney Disease. In: Lurbe E, Wühl E, editors. *Hypertension in Children*

and Adolescents: New Perspectives. Geneva, Switzerland: Springer International Publishing; 2019. 239-255 pp. doi:10.1007/978-3-030-18167-3.

18. Halbach S, Flynn J. Treatment of hypertension in children with chronic kidney disease. *Curr Hypertens Rep.* 2015;17(1):503. doi:10.1007/s11906-014-0503-3.

19. Kamath N, Iyengar A, George N, Luyckx VA. Risk Factors and Rate of Progression of CKD in Children. *Kidney Int Rep.* 2019;4(10):1472–1477. doi:10.1016/j.ekir.2019.06.004.

20. Becker BK, Zhang D, Soliman R, Pollock DM. Autonomic nerves and circadian control of renal function. *Auton Neurosci.* 2019;217:58–65. doi:10.1016/j.autneu.2019.01.003.

21. Vein AM, Voznesenskaia TG, Vorob'eva OV, et al., authors; Vein AM, editor. *Vegetativnye rasstroistva: klinika, diagnostika, lechenie [Vegetative disorders: clinic, diagnosis, treatment]*. Moscow: MIA; 2010. 637 p. (in Russian).

22. Neudakhin EV. Substantiation of energotropic therapy of vegetative disorders in children. *RMJ.* 2018;26(2-2):107–112. (in Russian).

23. Chutko LS, Surushkina Shu, Iakovenko EA, Kornishina TL. Vegetative-vascular dystonia in children and adolescents. Clinical and psychophysiological manifestations and therapy (review). *Praktika pediatria.* 2019;(3):17–21. (in Russian).

24. Majdannyyk VG, Mitjurajeva-Kornijko IO, Kuhta NM, Gnyloskurenko GV. *Vegetatyvni dysfunkcii' u ditej. Paroksyzmal'na vegetatyvna nedostatnist': monografija [Vegetative dysfunctions in children. Paroxysmal autonomic failure: monograph]*. Kyiv: Logos; 2017. 300 p. (in Ukrainian).

25. Borysova TP, Abaturov AE. Clinical manifestations and correction of autonomic dysfunction in children and adolescents. *Zdorov'e rebenka.* 2018;13(6):588–594. doi:10.22141/2224-0551.13.5.2018.143165. (in Russian).

26. Mikhieieva TM, Nechytailo DYU, Poniuk VV, Fomina TP. Features of the vegetative state and arterial pressure level in children with chronic gastroduodenal pathology. *Zaporozhye Medical Journal.* 2018;20(5):651–654. doi: 10.14739/2310-1210.2018.5.141662. (in Ukrainian).

27. Belyaeva LM, Kolupaeva EA, Korol SM, Mikulchik NV. Syndrome of vegetative dysfunction in children: myths and reality. *Meditsinskie novosti.* 2013;(5):5–15. (in Russian).

28. Zakharova IN, Tvorogova TM, Pshenichnikova II. Current guidelines for diagnosis and treatment of vegetative dystonia in children and adolescents. *Meditsinskiy sovet.* 2016;(16):116–123. doi:10.21518/2079-701X-2016-16-116-123. (in Russian).

29. Ostroumova OD, Kochetkov AI, Guseva TF, Zykova AA. Sympathetic nervous system activation in pathogenesis of development of essential hypertension and its role in target-organs damage in young and middle aged adults: the cardioprotective capabilities of Bisoprolol. *Kardiologiya.* 2018;58(3):63–72. doi:18087/cardio.2018.3.10100. (in Russian).

30. Agapitov LI, Cherepnina IV. Diagnostics and treatment of arterial hypertension in children and adolescents overview of new clinical guidelines of the American Academy of Pediatrics. *Rossiyskij vestnik perinatologii i pediatrii.* 2019;64(4):114–127. doi:10.21508/1027-4065-2019-64-4-114-127. (in Russian).

31. Writing Group Members, Mozaffarian D, Benjamin EJ, et al. Executive Summary: Heart Disease and Stroke Statistics –2016 Update: A Report From the American Heart Association. *Circulation.* 2016;133(4):447–454. doi:10.1161/CIR.0000000000000366.

32. Parati G, Esler M. The human sympathetic nervous system: its relevance in hypertension and heart failure. *Eur Heart J.* 2012;33(9):1058–1066. doi:10.1093/eurheartj/ehs041.

33. Kaur J, Young BE, Fadel PJ. Sympathetic Overactivity in Chronic Kidney Disease: Consequences and Mechanisms. *Int J Mol Sci.* 2017;18(8):1682. doi:10.3390/ijms18081682.

34. Makarova TP, Melnikova YuS. Endothelial dysfunction and elemental status in children with chronic kidney disease. *Rossiyskij vestnik perinatologii i pediatrii.* 2018;63(2):48–52. doi:10.21508/1027-4065-2018-63-2-48-52. (in Russian).

35. Carlstrom M, Montenegro MF. Therapeutic value of stimulating the nitrate-nitrite-nitric oxide pathway to attenuate oxidative stress and restore nitric oxide bioavailability in cardiorenal disease. *J Intern Med.* 2019;285(1):2–18. doi:10.1111/joim.12818.

36. Protopopov AA, Nesterenko OV, Borodulin VB, Shevchenko OV. Hyperhomocysteinemia as a predictor of the progression of chronic pyelonephritis. *Clinical Nephrology.* 2013;(6):33–36. (in Russian).

37. Martens CR, Kirkman DL, Edwards DG. The Vascular Endothelium in Chronic Kidney Disease: A Novel Target for Aerobic Exercise. *Exerc Sport Sci Rev.* 2016;44(1):12–19. doi:10.1249/JES.0000000000000065.

38. Reddy YS, Kiranmayi VS, Bitla AR, Krishna GS, Rao PV, Sivakumar V. Nitric oxide status in patients with chronic kidney disease. *Indian J Nephrol.* 2015;25(5):287–291. doi:10.4103/0971-4065.147376.

39. Chen J, Hamm LL, Mohler ER, et al. Interrelationship of Multiple Endothelial Dysfunction Biomarkers with Chronic Kidney Disease. *PLoS One.* 2015;10(7):e0132047. doi:10.1371/journal.pone.0132047.

40. Drożdż D, Łatka M, Drożdż T, Szeferko K, Kwinta P. Thrombomodulin as a New Marker of Endothelial Dysfunction in Chronic Kidney Disease in Children. *Oxid Med Cell Longev.* 2018;2018:1619293. doi:10.1155/2018/1619293.

41. Brooks ER, Haymond S, Rademaker A, et al. Contribution of symmetric dimethylarginine to GFR decline in pediatric chronic kidney disease. *Pediatr Nephrol.* 2018;33(4):697–704. doi:10.1007/s00467-017-3842-x.

42. Chien SJ, Lin IC, Hsu CN, Lo MH, Tain YL. Homocysteine and Arginine-to-Asymmetric Dimethylarginine Ratio Associated With Blood Pressure Abnormalities in Children With Early Chronic Kidney Disease. *Circ J.* 2015;79(9):2031–2037. doi:10.1253/circj.CJ-15-0412.

43. Inozemtseva ND, Zakharova NB, Rossolovsky AN. The importance of molecular markers in the study of endothelial dysfunction in patients with ICD (literature review). *Bulletin of Medical Internet Conferences.* 2015;5(6):902–905. (in Russian).

44. Noh MR, Jang HS, Kim J, Padanilam BJ. Renal Sympathetic Nerve-Derived Signaling in Acute and Chronic kidney Diseases. *Int J Mol Sci.* 2020;21(5):1647. doi:10.3390/ijms21051647.

45. Sata Y, Head GA, Denton K, May CN, Schlaich MP. Role of the Sympathetic Nervous System and Its Modulation in Renal Hypertension. *Front Med (Lausanne).* 2018;5:82. doi:10.3389/fmed.2018.00082.

46. Konradi AO. Interrelation between sympathetic and renin-angiotensin systems: Role in arterial hypertension. *Arterial'naya Gipertenziya.* 2012;18(6):577–583. doi:10.18705/1607-419X-2012-18-6-577-583. (in Russian).

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#### Нирки та вегетативна дисфункція у дітей і підлітків (частина I)

**Резюме.** У статті обговорюються механізми взаємодії, розвитку і прогресування серцево-судинних ускладнень у дітей та підлітків із хронічною хворобою нирок. Підкреслюється провідна роль вегетативної дисфункції в розвитку серцево-судинних порушень. Розглядаються механізми, за допомогою яких підвищення активності симпатичної частини вегетативної нервової системи призводить до ураження нирок. Взаємодія симпатичної нервової та ренін-ангіотензинової систем при формуванні порушень з боку серцево-судинної системи та

нирок розглядається як складова адаптаційно-приспосувального процесу організму. Універсальним патогенетичним фактором, який неодмінно супроводжує розвиток вегетативних дисфункцій та хронічної хвороби нирок у дітей і підлітків, є активація ренін-ангіотензинової системи. Спільні механізми розвитку кардіоренальних порушень визначають подальший односпрямований підхід до діагностики та лікування.

**Ключові слова:** діти; хронічна хвороба нирок; вегетативна дисфункція; артеріальна гіпертензія

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#### Почки и вегетативная дисфункция у детей и подростков (часть I)

**Резюме.** В статье обсуждаются механизмы взаимодействия, развития и прогрессирования сердечно-сосудистых осложнений у детей и подростков с хронической болезнью почек. Подчеркивается главенствующая роль вегетативной дисфункции в развитии сердечно-сосудистых нарушений. Рассматриваются механизмы, с помощью которых повышение активности симпатической части вегетативной нервной системы приводит к поражению почек. Взаимодействие симпатической нервной и ренин-ангиотензиновой систем при формировании нарушений со стороны сердечно-сосудистой системы

и почек рассматривается как составляющая адаптационно-приспособительного процесса организма. Универсальным патогенетическим фактором, который непременно сопровождает развитие вегетативных дисфункций и хронической болезни почек у детей и подростков, является активация ренин-ангиотензиновой системы. Общие механизмы развития кардиоренальных нарушений определяют дальнейший однонаправленный подход к диагностике и лечению.

**Ключевые слова:** дети; хроническая болезнь почек; вегетативная дисфункция; артериальная гипертензия

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