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Microbial-Derived Uremic Toxins: Role in the Pathogenesis of Comorbidities in Patients with Chronic Kidney Disease

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Aim: to analyze the significance of microbial-derived uremic toxins (MDUT) in the pathogenesis of comorbidities in patients with chronic kidney disease (CKD).
Key findings. Increased excretion of nitrogen metabolism products into the intestines of patients with CKD is associated with uremic dysbiosis, changes in the metabolic activity of the gut microbiota and the leaky gut syndrome, which largely cause the accumulation of MDUT in the internal environment of the body: indoxyl sulfate, p-cresyl sulfate, trimethylamine-N-oxide, etc. The results of recent studies allow to consider these metabolites as an independent risk factor for adverse outcomes in people with CKD due to the progression of renal dysfunction to the terminal stage, as well as frequent cardiovascular, neurological, bone mineral, nutritional and other complications.
Conclusion. MDUT are one of the key modulators of the pathogenetic relationship between the gut and kidneys. Therapeutic manipulations with intestinal microbiota can be considered a promising strategy for preventing complications associated with uremia.
Keywords: uremic toxins, gut microbiota, chronic kidney disease, comorbidities
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Уремические токсины микробного происхождения: роль в патогенезе коморбидной патологии у пациентов с хронической болезнью почек

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Цель публикации. Проанализировать значение уремических токсинов микробного происхождения (УТМП) в патогенезе коморбидной патологии у пациентов с хронической болезнью почек (ХБП).
Основные положения. Повышенная экскреция продуктов азотистого обмена в кишечник при ХБП ассоциирована с уремическим дисбиозом, изменениями метаболической активности микробиоты и синдромом повышенной эпителиальной проницаемости кишечника, которые во многом обусловливают накопление во внутренних средах организма УТМП: индоксил сульфата, р-крезил сульфата, триметиламин-N-оксида и др. Результаты исследований последних лет позволяют рассматривать эти соединения в качестве самостоятельного фактора риска неблагоприятных исходов у лиц с ХБП вследствие прогрессирования дисфункции почек до терминальной стадии, а также частых сердечно-сосудистых, неврологических, минерально-костных, алиментарных и других осложнений.
Выводы. УТМП являются одними из ключевых модуляторов перекрестной патогенетической взаимосвязи между кишечником и почками. Воздействие на кишечную микробиоту можно считать перспективной стратегией предупреждения осложнений, связанных с уремией.
Ключевые слова: уремические токсины, микробиота, хроническая болезнь почек, коморбидная патология
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Introduction

As the glomerular filtration rate decreases, the ability of the kidneys to remove metabolic products gradually decreases, which leads to the accumulation in the body of various substances called uremic toxins (UTs) [1]. Depending on the place of origin, UTs are classified into endogenous, exogenous or microbial [2].

Metabolomic studies have allowed to establish that in patients with CKD, a significant part of UTs is produced precisely with the participation of the intestinal microbiota [3, 4]. Indoxyl sulfate (IS), p-cresol sulfate (PCS), trimethylamine-N-oxide (TMAO), indole-3-acetic acid (IAA), p-cresyl glucuronide and phenylacetylglutamine are the most studied among all the currently identified MDUT [5]. It has been shown that MDUT exhibit biological activity and, therefore, can have a pathogenic effect on various types of cells. In individuals with CKD, the levels of MDUT and their precursors increase in proportion to the decline of kidney function, and are also closely associated with the risk of adverse outcomes due to frequent cardiovascular, neurological, bone mineral, nutritional and other complications [1, 6]. These organ-specific effects are mediated by various molecular mechanisms and signaling pathways, such as aryl hydrocarbon receptor (AhR)/nuclear factor-κB (NF-κB); mitogen activated protein kinase (MAPK) signaling; peroxisome proliferator-activated receptor γ coactivator 1-α (PGC-1α); heme oxygenase-1 (HO-1); nuclear factor erythroid 2-related factor 2 (Nrf2); runt-related transcription factor 2 (RUNX2); bone morphogenic protein 2 (BMP2); transcription factor Sp7 (Osterix); notch signaling; autophagy effectors; microRNAs; and reactive oxygen species induction [7].

This review briefly presents the current results of clinical and experimental studies demonstrating the possible pathogenetic role of MDUT in the progression of renal failure, as well as the development of comorbidities in patients with CKD.

Uremic dysbiosis

Given the key role of the kidneys in maintaining the body's homeostasis, it is natural that a violation of their function inevitably affects the functioning of other organs and systems, including the intestinal microbiota [8]. The results of numerous studies indicate that in patients with various nephropathies, the intestinal microbiota undergoes a transformation from a symbiotic state to a dysbiosis one, which is accompanied by changes in its metabolic activity [9].

It was found that in CKD, compared with healthy individuals, there is an increase in the number of *Proteobacteria* at the type level, while *Actinobacteria* and *Firmicutes* decrease. At the family level, there is an increase in the number of *Enterobacteria* and *Corynebacteria*, at the genus level — *Enterococci* and *Clostridium*. As CKD progresses, there is a tendency to increase the detected changes in the intestinal microbiota, as well as their differences depending on the etiology of renal failure and the variant of renal replacement therapy (hemodialysis, peritoneal dialysis or kidney transplantation) [10].

A decrease in the excretion of nitrogen metabolism products with urine, the main one among which is urea, leads to an increase in their entry into the gastrointestinal tract, which causes adaptive colonization of bacterial families expressing urease, uricase, tryptophanase and other enzymes involved in the synthesis of UTs [11]. Under the influence of microbial urease, urea undergoes hydrolysis with the formation of a large amount of ammonium hydroxide, resulting in an increase in the pH of the intraluminal contents of the intestine, irritation and local leukocyte infiltration of its mucous membrane, as well as hyperproduction of cytokines with subsequent violation of the structure and integrity of the skeleton and transmembrane proteins of tight junctions between neighboring enterocytes of the intestinal epithelium [12]. The effects of uremia are aggravated against the background of strict dietary restrictions of CKD patients, drug-induced polypharmacy, sedentary lifestyle, fluid intake restrictions and disorders of intestinal motility.

Enhanced generation of MDUT is also contributed by the proliferation of proteolytic bacterial species and entry in the colon of aromatic amino acids not absorbed into the small intestine [13]. It has been established that it is as a result of bacterial catabolism of tryptophan, phenylalanine, tyrosine and quaternary amines (betaine, L-carnitine and phosphatidylcholine) that the precursors of IS, PCS and TMAO are formed [14]. In addition, patients with CKD are characterized by a decrease in the number of bacteria synthesizing short-chain fatty acids, which have a wide range of immunoregulatory and metabolic functions [15].

The result of the above changes is the development of a leaky gut syndrome with uncontrolled transport into the bloodstream of a number of immunogenic substances generated by an aberrant microbiota, as well as activation of chronic systemic inflammation and oxidative stress, which are universal mechanisms for the development of many diseases [16, 17].

System effects of microbial-derived uremic toxins

Currently, there is no doubt that gut dysbiosis is an important factor in the pathogenesis of common socially significant diseases, such as obesity, diabetes mellitus, cardiovascular pathology and CKD [5, 18–20]. MDUT is considered as one of the major modulators of the connection between gut dysbiosis and these diseases occurrence and progression. The susceptibility of various tissues to UTs is determined by their type, interstitial concentration, as well as tissue perfusion and cellular permeability [21]. Unlike bacteria and their endotoxins, which induce inflammation and the synthesis of reactive oxygen species (ROS), the adverse effects of MDUT are caused, including, by their direct effect on cells [5, 7]. It has been established that some UTs, in particular, the advanced glycation end products (AGEs), have an effect on survival, migration and differentiation of endotheliocytes by linking with specific surface receptors (RAGE) [5]. In the study of H. Watanabe et al., it was shown that uptake by the renal tubules' epithelial cells some UTs (IS and PCS) can be mediated by organic anion transporters (OAT1 and OAT3) [22]. The ability of IS to affect a wide range of targets largely depends on the possibility of its transport through the plasma membrane and cytoplasmic contacts with AhR [21]. In addition, in patients with end stage renal disease, the low-molecular-weight water-soluble TMAO molecule is effectively removed by dialysis, in contrast to the protein-bound IS and PCS [23]. Thus, intracellular accumulation of MDUT or changes in their toxicokinetic in patients with CKD may be associated with varying degrees of negative effects described below.

Microbial-derived uremic toxins and chronic kidney disease progression

A growing number of publications indicate the important role of MDUT in the progression of renal failure. It was found that the accumulation of IS in the cells of the renal tubules disrupts their antioxidant system, and also enhances the renal expression of the genes involved in tubulointerstitial fibrosis, such as tissue metalloproteinase inhibitor, transforming growth factor β1 (TGF) and type I alpha-1 collagen [8, 24]. O. Ichii et al. *in vitro* examined toxic effect of IS on the cellular elements of the kidneys and found pathological changes of podocytes were, including wrinkling of the glomerular basement membrane, podocytes foot effacement and the formation of cytoplasmic vacuoles [25]. A significant effect on the structural and functional state of renal tissue has also been proven for other MDUT. A number of studies indicate that PCS and TMAO in experimental animals with CKD contribute to increased tubulointerstitial fibrosis and renal dysfunction [26, 27]. IAA, synthesized by intestinal bacteria from tryptophan, has similar effects by inducing the proinflammatory enzyme cyclooxygenase-2 and oxidative stress [28]. Epigenetic modification of some specific genes, apparently, may be another important nephrotoxic mechanism of MDUT. It has been shown that IS and PCS are involved in renal tissue remodeling, reducing the expression of nephroprotective factor klotho in the renal tubules [29, 30]. Elevated levels of MDUT in patients with CKD predict further progression of renal failure, cardiovascular events and all-causes mortality [31–33].

Cardiovascular diseases

Cardiovascular pathology is one of the leading causes of increased morbidity and mortality in patients with CKD. This is explained by high prevalence of both traditional and atypical cardiovascular risk factors, among which intestinal dysbiosis, MDUT and inflammation are considered the most significant [34]. The products of abnormal microbial metabolism in high concentrations have a direct toxic effect on cardiomyocytes, smooth muscle and vascular endothelial cells, participating in the remodeling of the myocardium and blood vessels, in the pathogenesis of atherosclerosis, hypertension and heart failure. Data obtained in *in vitro* experiments indicate that IS stimulates collagen synthesis by cardiac fibroblasts and cardiomyocyte hypertrophy. It is assumed that these effects are mediated by activation of mitogen activated protein kinase (MAPK) and the NF-kB signaling pathway [35]. It was found that PCS also causes significant structural and functional changes in the myocardium. PCS in CKD rats model led to an increase in the coefficient of cardiomyocyte apoptosis due to increased activity of caspase-3, as well as the production of reactive oxygen species and NADPH oxidase [36].

Intestinal dysbiosis contributes to the development of the most important CKD risk factor — arterial hypertension. N. Oshima et al. have shown that various types of UTs, including IS, activate bulbospinal neurons in the rostral ventrolateral medulla, a key area regulating blood pressure [37]. A number of studies have demonstrated that in patients with CKD, a high level of IS was associated with left ventricular myocardial hypertrophy, QT interval prolongation, increased risk of heart failure, and also serves as a strong predictor of overall and cardiovascular mortality [38].

Currently, there is strong evidence of the role of MDUT in accelerating the progression

of endothelial dysfunction, atherosclerosis and vascular calcification as a result of induction of systemic inflammation and oxidative stress [39]. In patients with various stages of CKD, a relationship was found between the content of some MDUT (IS, PCS) and carotid artery intima-media thickness, carotid-femoral pulse wave velocity and degree of aortic calcification [40]. IS can inhibit endothelial progenitor cells mediated neovascularization of ischemic tissues as well as enhance platelet aggregation and thrombus formation [41]. In patients with CKD higher blood levels of PCS significantly correlate with the severity of coronary arteriosclerosis, peripheral artery pathology and dysfunction of vascular access for hemodialysis [42, 43]. In this regard, the most convincing data are currently available for TMAO, the increased concentration of which, according to the results of large systematic review, was associated with a higher risk of major adverse cardiovascular events, as well as general and cardiovascular mortality [33]. Thus, individual and combined pathophysiological mechanisms involving MDUT may underlie the development and progression of cardiovascular pathology in individuals with CKD.

Nutritional status. Sarcopenia

The intestinal microbiota is necessary for the normal metabolism of nutrients and maintaining the energy balance of the body. Therefore, gut dysbiosis can make a significant contribution to the development of nutritional disorders in patients with CKD. Intestinal microflora affects the nutritional status of the host organism through microbial metabolites, systemic inflammation, appetite regulation, acidosis and various hormonal disorders. J. Hu et al. determined that anthropometric indicators, including handgrip strength, mid-upper arm circumference, mid-upper arm muscle circumference, and body mass index, in patients on dialysis negatively correlated with the level of conditionally pathogenic bacteria (*Escherichia* spp.) involved in the synthesis of UTs [44]. In turn, L. Caldiroli et al. found a positive association of serum PCS level with protein energy wasting syndrome in elderly patients with advanced CKD [45].

Currently, significant evidence has been obtained of that the MDUT is involved in the pathogenesis of uremic sarcopenia. The results of experimental studies show influence of MDUT on the structural and functional state of skeletal muscle tissue. E. Sato et al. visualized significant accumulation of IS and PCS in skeletal muscle of mice with adenine-induced CKD and established linear correlation between their levels and the severity of muscular atrophy [46]. IS has a direct toxic effect on myoblasts, reducing their viability and increasing cell apoptosis [47]. IS also induced mitochondrial dysfunction by decreasing the expression of PGC-1 and inducing autophagy in addition to decreasing mitochondrial membrane potential [48]. In addition, MDUT reduced the functional activity of myoblasts by premature termination of their differentiation, decrease myotubes formation or occurrence of their structural anomalies [49].

The results of clinical studies on this topic are controversial and differ depending on the type of studying UT [50, 51]. It should be noted that there are no convincing data for close relationship between IS and PCS levels and the severity of skeletal muscle loss in patients with CKD [46, 52].

Mineral bone disorders

Increasing evidence indicates that high levels of MDUT may play an important role in the pathogenesis of mineral bone disorders in patients with CKD, disrupting processes of the osteoblastogenesis and osteoclastogenesis, inhibiting bone mineralization, alkaline phosphatase activity, type I collagen transcription and the expression of other genes associated with bone formation [38, 53]. It is known that the uremic environment deteriorates the bone response to the parathyroid hormone (PTH) [54]. J. Hirata et al. found that dietary supplements with indole increase the level of IS in the blood and lead to further bone remodeling in rats after parathyroidectomy [55]. Concentration of IS in hemodialysis patients negatively correlates with markers of bone formation regardless of intact PTH level [56]. These data suggest that MDUT may worsen low bone metabolism by inhibiting bone formation through mechanisms unrelated to skeletal resistance to PTH. In pre-dialysis CKD patients, a relationship was found between serum concentration of IS, fibroblast growth factor-23 (FGF23) and the bone fibrosis [57, 58]. Another study showed that in 154 patients at CKD stages 2-5D, serum sclerostin (a predictor of increased fracture risk) independently correlates with IS, PCS and β2-microglobulin levels [59]. Thus, MDUT in patients with CKD may modify bone metabolism. However, the exact mechanisms of this influence remain unknown and require further study.

Anemia

MDUT blood accumulation leads to disruption of the synthesis of erythropoietin (EPO) by kidney peritubular fibroblasts due to suppression of EPO gene transcription [60]. In addition, IS inhibits the activation of hypoxia-inducible factor (HIF), which is the main regulator of hypoxic EPO production [61]. Another possible mechanism

of MDUT-induced anemia described in the study by Y. Adelibieke et al., is the suppression of intracellular pathways of EPO receptor activation, which may contribute to their resistance to EPO [62]. It has been established that IS *in vitro* stimulates eryptosis (programmed death of erythrocytes) [63], and also disrupts iron metabolism by regulating hepcidin synthesis [64]. Meanwhile, observational studies have not shown any association between MDUT levels and anemia in patients receiving dialysis treatment [65]. Future research in this field should determine the exact role of MDUT in the development of anemia in CKD.

Cognitive dysfunction

Despite the buffering function of the blood-brain barrier, decrease MDUT clearance by damaged kidneys leads to their gradual accumulation in brain tissues [46]. In patients with CKD MDUT have a direct neurotoxic effect with the progression of cognitive disorders [7]. IS is also found in the cerebrospinal fluid [66]. *In vitro* studies have shown that both low-molecular and protein-bound UTs reduce the viability of neuronal cells via inducing inflammation, oxidative stress and apoptosis [67, 68]. In mice with experimentally reproduced CKD, increase level of IS in the brainstem is associated with decrease of neurotransmitters content (norepinephrine, serotonin and dopamine), which was accompanied by various neurobehavioral disorders, including apathetic behavior, increased sensitivity to stress, decreased motor and exploratory activity and impaired spatial memory and coordination of movements [69]. In addition to direct neurotoxic effects MDUT play an important role in the pathogenesis of cerebrovascular diseases due to its effect on vascular tone and blood pressure [34]. Moreover, endothelial dysfunction and hemostatic disorders induced by UTs can cause cerebral microvascular dysfunction, which is a frequent cause of a significant proportion of cases of dementia and stroke [39]. In clinical studies, it has been proven that higher serum levels of IS and IAA in CKD individuals increase the risk of various cognitive disorders and dementia [7, 39, 70].

Other organ damage

Currently, the possible involvement of MDUT in the development of various metabolic disorders that often accompany CKD is being discussed. L. Koppe et al. showed that PCS may induce insulin resistance in cultured muscle and fat cells. Intraperitoneal injections of PCS for a 4 weeks similarly induced insulin resistance with ectopic lipid redistribution in skeletal muscle and liver in mice with normal renal function [71]. In rats with subtotal nephrectomy, the accumulation of IS in adipose tissue is accompanied by oxidative stress, an increase in the content of lipid peroxidation products and activate insulin signaling [72]. The hepatotoxic effect of MDUT is manifested in their ability to activate *in vitro* apoptosis of hepatocytes [73]. MDUT are probably associated with the development of uremic pruritus in patients with end-stage CKD, since an increase the dialysis dose, as well as the use high-flux dialyzers and biocompatible membranes often results to an improvement in symptoms [74]. It is assumed that IS may also be involved in lung tissue damage in renal failure [75].

The results of numerous studies indicate that dietary changes, the use of drugs that normalize the intestinal microflora (prebiotics, probiotics, synbiotics), sorbents (AST-120) and some other therapeutic interventions can reduce the level of MDUT and the activity of chronic systemic inflammation in patients with CKD [6, 8, 12, 17]. Although some of these approaches seem promising and indirectly confirm the pathogenic role of MDUT, currently none of them has shown a significant effect on cardiovascular outcomes or mortality in randomized controlled trials and therefore cannot be recommended for clinical use.

Conclusion

Advances in modern science have made it possible to establish that MDUT are one of the key modulators of the cross pathogenetic relationship between the intestine and kidneys, and effort to reduce their concentration seems to be a reasonable strategy for preventing complications associated with uremia. Thus, exposure to the intestinal microbiota can become a widely available non-invasive therapeutic approach with the potential to reach a large number of patients. However, further large-scale clinical trials are needed to confirm the safety and efficacy of these approaches in improving outcomes and survival in patients with CKD.

References / Литература

1. *Vanholder R., Fouque D., Glorieux G., Heine G.H., Kanbay M., Mallamaci F., et al.* European Renal Association European Dialysis; Transplant Association (ERA-EDTA) European Renal; Cardiovascular Medicine (EURECA-m) working group. Clinical management of the uraemic syndrome in chronic kidney disease. *Lancet Diabetes Endocrinol*. 2016;4(4):360–73. DOI: 10.1016/S2213-8587(16)00033-4
2. *Koppe L., Fouque D., Soulage C.O.* The role of gut microbiota and diet on uremic retention solutes production in the context of chronic kidney disease. *Toxins (Basel)*. 2018;10(4):155. DOI: 10.3390/toxins10040155
3. *Aronov P.A., Luo F.J., Plummer N.S., Quan Z., Holmes S., Hostetter T.H., et al.* Colonic contribution to uremic solutes. *J Am Soc Nephrol*. 2011;22(9):1769–76. DOI: 10.1681/ASN.2010121220
4. *Mishima E., Fukuda S., Mukawa C., Yuri A., Kanemitsu Y., Matsumoto Y., et al.* Evaluation of the impact of gut microbiota on uremic solute accumulation by a CE-TOFMS-based metabolomics approach. *Kidney Int*. 2017;92(3):634–45. DOI: 10.1016/j.kint.2017.02.011
5. *Vanholder R., Pletinck A., Schepers E., Glorieux G.* Biochemical and clinical impact of organic uremic retention solutes: A comprehensive update. *Toxins (Basel)*. 2018;10(1):33. DOI: 10.3390/toxins10010033
6. *Kim S.M., Song I.H.* The clinical impact of gut microbiota in chronic kidney disease. *Korean J Intern Med*. 2020;35(6):1305–16. DOI: 10.3904/kjim.2020.411
7. *Chao C.T., Lin S.H.* Uremic toxins and frailty in patients with chronic kidney disease: A molecular insight. *Int J Mol Sci*. 2021;22(12):6270. DOI: 10.3390/ijms22126270
8. *Rysz J., Franczyk B., Ławiński J., Olszewski R., Ciałkowska-Rysz A., Gluba-Brzózka A.* The impact of CKD on uremic toxins and gut microbiota. *Toxins (Basel)*. 2021;13(4):252. DOI: 10.3390/toxins13040252
9. *Лукичев Б.Г., Румянцев А.Ш., Акименко В.* Микробиота кишечника и хроническая болезнь почек. Сообщение первое. *Нефрология*. 2018;22(4):57–73. [*Lukichev B.G., Rumyantsev A.S., Akimenko V.* Colonic microbiota and chronic kidney disease. Message one. *Nephrology (Saint-Petersburg)*. 2018;22(4):57–73 (In Russ.)]. DOI: 10.24884/1561-6274-2018-22-4-57-73
10. *Lau W.L., Savoj J., Nakata M.B., Vaziri N.D.* Altered microbiome in chronic kidney disease: Systemic effects of gut-derived uremic toxins. *Clin Sci (Lond)*. 2018;132(5):509–22. DOI: 10.1042/CS20171107
11. *Wong J., Piceno Y.M., DeSantis T.Z., Pahl M., Andersen G.L., Vaziri N.D.* Expansion of urease- and uricase-containing, indole- and p-cresol-forming and contraction of short-chain fatty acid-producing intestinal microbiota in ESRD. *Am J Nephrol*. 2014;39(3):230–7. DOI: 10.1159/000360010
12. *Vaziri N., Zhao Y., Pahl M.* Altered intestinal microbial flora and impaired epithelial barrier structure and function in CKD: The nature, mechanisms, consequences and potential treatment. *Nephrol Dial Transplant*. 2016;31(5):737–46. DOI: 10.1093/ndt/gfv095
13. *Mafra D., Borges N.A., Cardozo L.F.M.F., Anjos J.S., Black A.P., Moraes C., et al.* Red meat intake in chronic kidney disease patients: Two sides of the coin. *Nutrition*. 2018;46:26–32. DOI: 10.1016/j.nut.2017.08.015
14. *Joossens M., Faust K., Gryp T., Nguyen A.T.L., Wang J., Eloot S., et al.* Gut microbiota dynamics and uraemic toxins: One size does not fit all. *Gut*. 2019;68(12):2257–60. DOI: 10.1136/gutjnl-2018-317561
15. *Пятченков М.О., Марков А.Г., Румянцев А.Ш.* Структурно-функциональные нарушения кишечного барьера и хроническая болезнь почек. Обзор литературы. Часть I. *Нефрология*. 2022;26(1):10–26. [*Pyatchenkov M.O., Markov A.G., Rumyantsev A.S.* Structural and functional intestinal barrier abnormalities and chronic kidney disease. Literature review. Part I. *Nephrology (Saint-Petersburg)*. 2022;26(1):10–26 (In Russ.)]. DOI: 10.36485/1561-6274-2022-26-1-10-26
16. *Glorieux G., Gryp T., Perna A.* Gut-derived metabolites and their role in immune dysfunction in chronic kidney disease. *Toxins (Basel)*. 2020;12(4):245. DOI: 10.3390/toxins12040245
17. *Пятченков М.О., Румянцев А.Ш., Щербаков Е.В., Марков А.Г.* Структурно-функциональные нарушения кишечного барьера и хроническая болезнь почек. Обзор литературы. Часть II. *Нефрология*. 2022;26(2):46–64. [*Pyatchenkov M.O., Rumyantsev A.S., Sherbakov E.V., Markov A.G.* Structural and functional intestinal barrier abnormalities and chronic kidney disease. Literature review. Part II. *Nephrology (Saint-Petersburg)*. 2022;26(2):46–64 (In Russ.)]. DOI: 10.36485/1561-6274-2022-26-2-46-64
18. *Yang G., Wei J., Liu P., Zhang Q., Tian Y., Hou G., et al.* Role of the gut microbiota in type 2 diabetes and related diseases. *Metabolism*. 2021;117:154712. DOI: 10.1016/j.metabol.2021.154712
19. *Chakaroun R.M., Massier L., Kovacs P.* Gut microbiome, intestinal permeability, and tissue bacteria in metabolic disease: Perpetrators or bystanders? *Nutrients*. 2020;12(4):1082. DOI: 10.3390/nu12041082
20. *Novakovic M., Rout A., Kingsley T., Kirchoff R., Singh A., Verma V., et al.* Role of gut microbiota in cardiovascular diseases. *World J Cardiol*. 2020;12(4):110–22. DOI: 10.4330/wjc.v12.i4.110
21. *Graboski A.L., Redinbo M.R.* Gut-derived protein-bound uremic toxins. *Toxins (Basel)*. 2020;12(9):590. DOI: 10.3390/toxins12090590
22. *Watanabe H., Miyamoto Y., Otagiri M., Maruyama T.* Update on the pharmacokinetics and redox properties of protein-bound uremic toxins. *J Pharm Sci*. 2011;100(9):3682–95. DOI: 10.1002/jps.22592
23. *Bain M.A., Faull R., Fornasini G., Milne R.W., Evans A.M.* Accumulation of trimethylamine and trimethylamine-N-oxide in end-stage renal disease patients undergoing haemodialysis. *Nephrol Dial Transplant*. 2006;21(5):1300–4. DOI: 10.1093/ndt/gfk056
24. *Miyazaki T., Ise M., Seo H., Niwa T.* Indoxyl sulfate increases the gene expressions of TGF-beta 1, TIMP-1 and pro-alpha 1(I) collagen in uremic rat kidneys. *Kidney Int Suppl*. 1997;62:S15–22.
25. *Ichii O., Otsuka-Kanazawa S., Nakamura T., Ueno M., Kon Y., Chen W, et al.* Podocyte injury caused by indoxyl sulfate, a uremic toxin and aryl-hydrocarbon receptor ligand. *PLoS One*. 2014;9(9):e108448. DOI: 10.1371/journal.pone.0108448
26. *Tang W.H., Wang Z., Kennedy D.J., Wu Y., Buffa J.A., Agatisa-Boyle B., et al.* Gut microbiota-dependent trimethylamine N-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease. *Circ Res*. 2015;116(3):448–55. DOI: 10.1161/CIRCRESAHA.116.305360
27. *Watanabe H., Miyamoto Y., Honda D., Tanaka H., Wu Q., Endo M., et al.* p-Cresyl sulfate causes renal tubular cell damage by inducing oxidative stress by activation of NADPH oxidase. *Kidney Int*. 2013;83(4):582–92. DOI: 10.1038/ki.2012.448
28. *Satoh M., Hayashi H., Watanabe M., Ueda K., Yamato H., Yoshioka T., et al.* Uremic toxins overload accelerates renal damage in a rat model of chronic renal failure. *Nephron Exp Nephrol*. 2003;95(3):e111–8. DOI: 10.1159/000074327
29. *Sun C.Y., Chang S.C., Wu M.S.* Suppression of Klotho expression by protein-bound uremic toxins is associated with increased DNA methyltransferase expression and DNA hypermethylation. *Kidney Int*. 2012;81(7):640–50. DOI: 10.1038/ki.2011.445
30. *Shimizu H., Bolati D., Adijiang A., Adelibieke Y., Muteliefu G., Enomoto A., et al.* Indoxyl sulfate downregulates renal expression of Klotho through production of ROS and activation of nuclear factor-κB. *Am J Nephrol*. 2011;33(4):319–24. DOI: 10.1159/000324885
31. *Dou L., Sallée M., Cerini C., Poitevin S., Gondouin B., Jourde-Chiche N., et al.* The cardiovascular effect of the

uremic solute indole-3 acetic acid. *J Am Soc Nephrol*. 2015;26(4):876–87. DOI: 10.1681/ASN.2013121283
32. *Wu I.W., Hsu K.H., Lee C.C., Sun C.Y., Hsu H.J., Tsai C.J., et al.* p-Cresyl sulphate and indoxyl sulphate predict progression of chronic kidney disease. *Nephrol Dial Transplant*. 2011;26(3):938–47. DOI: 10.1093/ndt/gfq580
33. *Sanchez-Gimenez R., Ahmed-Khodja W., Molina Y., Peiró O.M., Bonet G., Carrasquer A., et al.* Gut microbiota-derived metabolites and cardiovascular disease risk: A systematic review of prospective cohort studies. *Nutrients*. 2022;14(13):2654. DOI: 10.3390/nu14132654
34. *Huang Y., Xin W., Xiong J., Yao M., Zhang B., Zhao J.* The intestinal microbiota and metabolites in the gut-kidney-heart axis of chronic kidney disease. *Front Pharmacol*. 2022;13:837500. DOI: 10.3389/fphar.2022.837500
35. *Lekawanvijit S., Adrahtas A., Kelly D.J., Kompa A.R., Wang B.H., Krum H.* Does indoxyl sulfate, a uraemic toxin, have direct effects on cardiac fibroblasts and myocytes? *Eur Heart J*. 2010;31(14):1771–9. DOI: 10.1093/eurheartj/ehp574
36. *Han H., Zhu J., Zhu Z., Ni J., Du R., Dai Y., et al.* p-Cresyl sulfate aggravates cardiac dysfunction associated with chronic kidney disease by enhancing apoptosis of cardiomyocytes. *J Am Heart Assoc*. 2015;4(6):e001852. DOI: 10.1161/JAHA.115.001852
37. *Oshima N., Onimaru H., Matsubara H., Uchida T., Watanabe A., Takechi H., et al.* Uric acid, indoxyl sulfate, and methylguanidine activate bulbospinal neurons in the RVLM via their specific transporters and by producing oxidative stress. *Neuroscience*. 2015;304:133–45. DOI: 10.1016/j.neuroscience.2015.07.055
38. *Fujii H., Goto S., Fukagawa M.* Role of uremic toxins for kidney, cardiovascular, and bone dysfunction. *Toxins (Basel)*. 2018;10(5):202. DOI: 10.3390/toxins10050202
39. *Assem M., Lando M., Grissi M., Kamel S., Massy Z.A., Chillon J.M., et al.* The impact of uremic toxins on cerebrovascular and cognitive disorders. *Toxins (Basel)*. 2018;10(7):303. DOI: 10.3390/toxins10070303
40. *Rodrigues F.G., Ormanji M.S., Heilberg I.P., Bakker S.J.L., de Borst M.H.* Interplay between gut microbiota, bone health and vascular calcification in chronic kidney disease. *Eur J Clin Invest*. 2021;51(9):e13588. DOI: 10.1111/eci.13588
41. *Obokata M., Kurosawa K., Ishida H., Ito K., Ogawa T., Ando Y., et al.* Echocardiography-based pressure-volume loop assessment in the evaluation for the effects of indoxyl sulfate on cardiovascular function. *J Echocardiogr*. 2019;17(1):35–43. DOI: 10.1007/s12574-018-0385-5
42. *Wang C.P., Lu L.F., Yu T.H., Hung W.C., Chiu C.A., Chung F.M., et al.* Serum levels of total p-cresylsulphate are associated with angiographic coronary atherosclerosis severity in stable angina patients with early stage of renal failure. *Atherosclerosis*. 2010;211(2):579–83. DOI: 10.1016/j.atherosclerosis.2010.03.036
43. *Lin C.J., Pan C.F., Liu H.L., Chuang C.K., Jayakumar T., Wang T.J., et al.* The role of protein-bound uremic toxins on peripheral artery disease and vascular access failure in patients on hemodialysis. *Atherosclerosis*. 2012;225(1):173–9. DOI: 10.1016/j.atherosclerosis.2012.07.012
44. *Hu J., Zhong X., Liu Y., Yan J., Zhou D., Qin D., et al.* Correlation between intestinal flora disruption and protein-energy wasting in patients with end-stage renal disease. *BMC Nephrol*. 2022;23(1):130. DOI: 10.1186/s12882-022-02762-2
45. *Caldiroli L., Armelloni S., Eskander A., Messa P., Rizzo V., Margiotta E., et al.* Association between the uremic toxins indoxyl-sulfate and p-cresyl-sulfate with sarcopenia and malnutrition in elderly patients with advanced chronic kidney disease. *Exp Gerontol*. 2021;147:111266. DOI: 10.1016/j.exger.2021.111266
46. *Sato E., Saigusa D., Mishima E., Uchida T., Miura D., Morikawa-Ichinose T., et al.* Impact of the oral adsorbent AST-120 on organ-specific accumulation of uremic toxins: LC-MS/MS and MS imaging techniques. *Toxins (Basel)*. 2017;10(1):19. DOI: 10.3390/toxins10010019
47. *Rodrigues G.G.C., Dellê H., Brito R.B.O., Cardoso V.O., Fernandes K.P.S., Mesquita-Ferrari R.A., et al.* Indoxyl sulfate contributes to uremic sarcopenia by inducing apoptosis in myoblasts. *Arch Med Res*. 2020;51(1):21–9. DOI: 10.1016/j.arcmed.2019.12.020
48. *Enoki Y., Watanabe H., Arake R., Fujimura R., Ishiodori K., Imafuku T., et al.* Potential therapeutic interventions for chronic kidney disease-associated sarcopenia via indoxyl sulfate-induced mitochondrial dysfunction. *J Cachexia Sarcopenia Muscle*. 2017;8(5):735–47. DOI: 10.1002/jcsm.12202
49. *Changchien C.Y., Lin Y.H., Cheng Y.C., Chang H.H., Peng Y.S., Chen Y.* Indoxyl sulfate induces myotube atrophy by ROS-ERK and JNK-MAFbx cascades. *Chem Biol Interact*. 2019;304:43–51. DOI: 10.1016/j.cbi.2019.02.023
50. *Yabuuchi J., Ueda S., Yamagishi S.I., Nohara N., Nagasawa H., Wakabayashi K., et al.* Association of advanced glycation end products with sarcopenia and frailty in chronic kidney disease. *Sci Rep*. 2020;10(1):17647. DOI: 10.1038/s41598-020-74673-x
51. *Saoi M., Li A., McGlory C., Stokes T., von Allmen M.T., Phillips S.M., et al.* Metabolic perturbations from step reduction in older persons at risk for sarcopenia: Plasma biomarkers of abrupt changes in physical activity. *Metabolites*. 2019;9(7):134. DOI: 10.3390/metabo9070134
52. *Margiotta E., Caldiroli L., Callegari M.L., Miragoli F., Zanoni F., Armelloni S., et al.* Association of sarcopenia and gut microbiota composition in older patients with advanced chronic kidney disease, investigation of the interactions with uremic toxins, inflammation and oxidative stress. *Toxins (Basel)*. 2021;13(7):472. DOI: 10.3390/toxins13070472
53. *Shyu J.F., Liu W.C., Zheng C.M., Fang T.C., Hou Y.C., Chang C.T., et al.* Toxic effects of indoxyl sulfate on osteoclastogenesis and osteoblastogenesis. *Int J Mol Sci*. 2021;22(20):11265. DOI: 10.3390/ijms222011265
54. *Nii-Kono T., Iwasaki Y., Uchida M., Fujieda A., Hosokawa A., Motojima M., et al.* Indoxyl sulfate induces skeletal resistance to parathyroid hormone in cultured osteoblastic cells. *Kidney Int*. 2007;71(8):738–43. DOI: 10.1038/sj.ki.5002097
55. *Hirata J., Hirai K., Asai H., Matsumoto C., Inada M., Miyaura C., et al.* Indoxyl sulfate exacerbates low bone turnover induced by parathyroidectomy in young adult rats. *Bone*. 2015;79:252–8. DOI: 10.1016/j.bone.2015.06.010
56. *Goto S., Fujii H., Hamada Y., Yoshiya K., Fukagawa M.* Association between indoxyl sulfate and skeletal resistance in hemodialysis patients. *Ther Apher Dial*. 2010;14(4):417–23. DOI: 10.1111/j.1744-9987.2010.00813.x
57. *Barreto F.C., Barreto D.V., Canziani M.E., Tomiyama C., Higa A., Mozar A., et al.* Association between indoxyl sulfate and bone histomorphometry in pre-dialysis chronic kidney disease patients. *J Bras Nefrol*. 2014;36(3):289–96. DOI: 10.5935/0101-2800.20140042
58. *Lin C.J., Pan C.F., Chuang C.K., Liu H.L., Sun F.J., Wang T.J., et al.* Association of indoxyl sulfate with fibroblast growth factor 23 in patients with advanced chronic kidney disease. *Am J Med Sci*. 2014;347(5):370–6. DOI: 10.1097/MAJ.0b013e3182989f26
59. *Desjardins L., Liabeuf S., Oliveira R.B., Louvet L., Kamel S., Lemke H.D., et al.; European Uremic Toxin (EUTox) Work Group.* Uremic toxicity and sclerostin in chronic kidney disease patients. *Nephrol Ther*. 2014;10(6):463–70. DOI: 10.1016/j.nephro.2014.04.002
60. *Chiang C.K., Tanaka T., Inagi R., Fujita T., Nangaku M.* Indoxyl sulfate, a representative uremic toxin, suppresses erythropoietin production in a HIF-dependent manner. *Lab Invest*. 2011;91(11):1564–71. DOI: 10.1038/labinvest.2011.114
61. *Hamza E., Metzinger L., Metzinger-Le Meuth V.* Uremic toxins affect erythropoiesis during the course of

chronic kidney disease: A review. *Cells*. 2020;9(9):2039. DOI: 10.3390/cells9092039
62. *Adelibieke Y., Shimizu H., Saito S., Mironova R., Niwa T.* Indoxyl sulfate counteracts endothelial effects of erythropoietin through suppression of Akt phosphorylation. *Circ J*. 2013;77(5):1326–36. DOI: 10.1253/circj.cj-12-0884
63. *Ahmed M.S., Abed M., Voelkl J., Lang F.* Triggering of suicidal erythrocyte death by uremic toxin indoxyl sulfate. *BMC Nephrol*. 2013;14:244. DOI: 10.1186/1471-2369-14-244
64. *Hamano H., Ikeda Y., Watanabe H., Horinouchi Y., Izawa-Ishizawa Y., Imanishi M., et al.* The uremic toxin indoxyl sulfate interferes with iron metabolism by regulating hepcidin in chronic kidney disease. *Nephrol Dial Transplant*. 2018;33(4):586–97. DOI: 10.1093/ndt/gfx252
65. *Bataille S., Pelletier M., Sallée M., Berland Y., McKay N., Duval A., et al.* Indole 3-acetic acid, indoxyl sulfate and paracresyl-sulfate do not influence anemia parameters in hemodialysis patients. *BMC Nephrol*. 2017;18(1):251. DOI: 10.1186/s12882-017-0668-5
66. *Sun C.Y., Li J.R., Wang Y.Y., Lin S.Y., Ou Y.C., Lin C.J., et al.* Indoxyl sulfate caused behavioral abnormality and neurodegeneration in mice with unilateral nephrectomy. *Aging (Albany NY)*. 2021;13(5):6681–701. DOI: 10.18632/aging.202523
67. *Watanabe K., Sato E., Mishima E., Watanabe M., Abe T., Takahashi N., et al.* Effect of uremic toxins on hippocampal cell damage: Analysis *in vitro* and in rat model of chronic kidney disease. *Heliyon*. 2021;7(2):e06221. DOI: 10.1016/j.heliyon.2021.e06221
68. *Lin Y.T., Wu P.H., Tsai Y.C., Hsu Y.L., Wang H.Y., Kuo M.C., et al.* Indoxyl sulfate induces apoptosis through oxidative stress and mitogen-activated protein kinase signaling pathway inhibition in human astrocytes. *J Clin Med*. 2019;8(2):191. DOI: 10.3390/jcm8020191
69. *Karbowska M., Hermanowicz J.M., Tankiewicz-Kwedlo A., Kalaska B., Kaminski T.W., Nosek K., et al.* Neurobehavioral effects of uremic toxin-indoxyl sulfate in the rat model. *Sci Rep*. 2020;10(1):9483. DOI: 10.1038/s41598-020-66421-y
70. *Liabeuf S., Pepin M., Franssen C.F.M., Viggiano D., Carriazo S., Gansevoort R.T., et al.; CONNECT Action (Cognitive Decline in Nephro-Neurology European Cooperative Target).* Chronic kidney disease and neurological disorders: Are uraemic toxins the missing piece of the puzzle? *Nephrol Dial Transplant*. 2021;37(Suppl 2):ii33–44. DOI: 10.1093/ndt/gfab223
71. *Koppe L., Pillon N.J., Vella R.E., Croze M.L., Pelletier C.C., Chambert S., et al.* p-Cresyl sulfate promotes insulin resistance associated with CKD. *J Am Soc Nephrol*. 2013;24(1):88–99. DOI: 10.1681/ASN.2012050503
72. *Minakuchi H., Wakino S., Hosoya K., Sueyasu K., Hasegawa K., Shinozuka K., et al.* The role of adipose tissue asymmetric dimethylarginine/dimethylarginine dimethylaminohydrolase pathway in adipose tissue phenotype and metabolic abnormalities in subtotally nephrectomized rats. *Nephrol Dial Transplant*. 2016;31(3):413–23. DOI: 10.1093/ndt/gfv367
73. *Deng M., Li X., Li W., Gong J., Zhang X., Ge S., et al.* Short-chain fatty acids alleviate hepatocyte apoptosis induced by gut-derived protein-bound uremic toxins. *Front Nutr*. 2021;8:756730. DOI: 10.3389/fnut.2021.756730
74. *Martin C.E., Clotet-Freixas S., Farragher J.F., Hundemer G.L.* Have we just scratched the surface? A narrative review of uremic pruritus in 2020. *Can J Kidney Health Dis*. 2020;7:2054358120954024. DOI: 10.1177/2054358120954024
75. *Yabuuchi N., Sagata M., Saigo C., Yoneda G., Yamamoto Y., Nomura Y., et al.* Indoxyl sulfate as a mediator involved in dysregulation of pulmonary aquaporin-5 in acute lung injury caused by acute kidney injury. *Int J Mol Sci*. 2016;18(1):11. DOI: 10.3390/ijms18010011

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