УДК: 616.61-002.2:616-018

THE ROLE OF PODOCYTIC DYSFUNCTION IN THE PROGRESSION OF CHRONIC GLOMERULONEPHRITIS

Qodirova Sh.A., Raxmatov A.M., Xujaniyazova N.K.*

Tashkent Medical Academy, Tashkent city, Uzbekistan

*Public Health College named after Abu Ali ibn Sino, Tashkent city, Uzbekistan**

РЕЗЮМЕ

Роль подоцитарной дисфункции в прогрессировании хронического гломерулонефрита

Кодирова Ш.А., Рахматов А.М., Хужаниязова Н.К.*

Ташкентская Медицинская Академия, г. Ташкент, Узбекистан

Техникум общественного здоровья имени Абу Али ибн Сино, г. Ташкент, Узбекистан*

В обзоре рассмотрены механизмы повреждения подоцитов, лежащие в основе развития протеинурии и прогрессирования гломерулосклероза при хроническом гломерулонефрите, представлены результаты экспериментальных и клинических исследований по данным вопросам. Авторами описан спектр маркеров подоцитарного повреждения, освещены методы их инвазивной и неинвазивной оценки, проанализирована взаимосвязь их уровня с выраженностью протеинурии и дисфункции почек, рассмотрены перспективы исследования подоцитарных белков в моче для оценки тяжести гломерулярного повреждения, риска развития гломерулосклероза.

Ключевые слова: *подоцитурия, нефринурия, подоцитарная дисфункция, подоцитопения, хронический гломерулонефрит.*

ХУЛОСА

Сурункали гломерулонефрит ривожланишида подоцитар дисфункциянинг роли

Қодирова Ш.А., Рахматов А.М., Хужаниязова Н.К.*

Тошкент Тиббиёт Академияси, Тошкент ш., Ўзбекистон

Абу Али ибн Сино номидаги Жамоат саломатлик техникуми, Тошкент ш., Ўзбекистон*

Қуйидаги мақолада сурункали гломерулонефритда протеинурия ривожланиши ва гломерулосклерознинг ривожланишига асос бўлган подоцитларнинг шикастланиш механизмлари ёритиб берилади, ушбу масала бўйича експериментал ва клиник тадқиқотлар натижаларини тақдим қилинади. Муаллифлар подоцитар шикастланиш белгиларининг спектрини тавсифладилар, уларни инвазив ва ноинвазив баҳолаш усулларини

таъкидладилар, уларнинг даражасининг протеинурия ва буйрак функцияси бузилишининг оғирлиги билан боғлиқлигини таҳлил қилдилар, сийдикда подоцитар оқсилларни ўрганиш истиқболларини кўриб чиқдилар.

Калит сўзлар: *подоцитурия, нефринурия, подоцитар дисфункция, подоцитопения, сурункали гломерулонефрит.*

SUMMARY

The role of podocytic dysfunction in the progression of chronic glomerulonephritis

Qodirova Sh.A., Raxmatov A.M., Xujaniyazova N.K.*

Tashkent Medical Academy, Tashkent city, Uzbekistan

Public Health College named after Abu Ali ibn Sino, Tashkent city, Uzbekistan*

The review considers the mechanisms of podocyte damage underlying the development of proteinuria and progression of glomerulosclerosis in chronic glomerulonephritis and presents the results experimental and clinical studies on these issues. It is described how, under the action of various immune and non-immune factors, podocytes form a stereotypic response to damage consisting in rearrangement of actin cytoskeleton, flattening of stem processes, detachment of podocytes from the glomerular basal membrane and the appearance of specific podocytic proteins and/or whole cells in the urine (podocyturia). Massive podocyturia in limited Proliferative ability of podocytes contributes to the reduction of their total mass in the glomerulus (podocytopenia) and the development of glomerulosclerosis. The authors describe the spectrum of markers of podocytic damage, highlight the methods of their invasive and noninvasive assessment, analyze the relationship of their level with the severity of proteinuria and renal dysfunction, consider Prospects of the study of podocytic proteins in urine to assess the severity of glomerular damage, the risk of glomerulosclerosis.

Key words: *podocyturia, nephrinuria, podocytic dysfunction, podocytopenia, chronic glomerulonephritis.*

Chronic glomerulonephritis (CGN) is a disease in which inflammation develops in the tubules and progresses as a result of limited capacity of glomerular structures for regeneration. The central link in the development of proteinuria (PU), the severity of which is still considered as a clinical equivalent of the activity/progression of CGN, is damage to the podocyte, a key component of the filtration barrier [1, 2]. Performing an important role in maintaining the structure and function of the renal glomerulus in normal, podocytes are of paramount importance in its damage and the progression of renal disease. In 2002, M.R. Pollak united a group of congenital diseases occurring with primary damage to podocytes and nephrotic syndrome (NS), the term "true podocytopathies" [3]. The "true podocytopathies" include disease of minimal changes, focal segmental glomerulosclerosis and membranous nephropathy. It is now shown that changes in

podocyte structure and function are detected in various morphological forms of glomerulonephritis (GN), proceeding with large PU [4]. The stereotypic response of podocyte to a variety of damaging factors (immune, hemodynamic, metabolic) is a decrease in the expression of structural proteins of slit diaphragm, which leads to changes in cytoskeleton, podocyte shape, impaired adhesion to glomerular basal membrane (GBM) with podocyte sloughing into the urinary space, resulting in disruption of glomerular filter barrier function and development of PU [5, 6].

Basic functions of podocytes

The glomerular filtration barrier is of paramount importance in limiting glomerular permeability, primarily to albumin and other blood plasma proteins. It consists of the basal capillary membrane, a monolayer of endothelial cells lining the glomerular filter from the inside, and a layer of podocytes that line the glomerular filter from the outside, from the urinary space side [7]. Podocytes and podocyte-associated molecules are currently attributed the most importance in the mechanisms of glomerular filter permeability disruption and the development of PU [8]. In addition to the formation of filtration barrier, podocytes perform a number of other important functions: they participate in maintaining the structure of capillary loops, counteract intracapillary hydrostatic pressure; provide endocytosis of filter proteins and immunoglobulins; participate in processes of type IV collagen synthesis and GBM repair; take part in immune response by expressing Toll-R4, B7.1 (CD80); ensure the normal function of other glomerular cells (mesangial, endothelial) through the production of several growth factors, in particular, vascular endothelial growth factor (VEGF) [2, 7, 9-11].

Podocyte response to damage

Damage to podocytes, which, according to the location of these cells outside the capillary wall, leads to GBM disruption, underlies the development of PU and NS [12]. Structural signs of podocyte damage are loss of small processes (stalk prolapse), microvillous transformation of apical surface, hypertrophy, epithelial-mesenchymal transdifferentiation, and cell apoptosis. The earliest sign of podocytic damage, detectable only by electron microscopy, is podocyte pedicle proliferation. This process occurs due to rearrangement of actin cytoskeleton, redistribution of actin microfilaments, as a result of which podocyte processes lose their shape. As a result of podocyte stems/branches proliferating, the slit diaphragm is stretched, the interpodocyte space is enlarged, and PU occurs. There is a point of view that podocyte stalks prolapse is an adaptive reaction to limit the glomerular permeability to the protein and prevent more serious damage - the formation of of "bare" areas of GBM [5, 13]. Podocyte peduncles proliferate in two stages. At the first stage, the podocyte processes lose their shape [14]. The loss of slit diaphragm or its apical displacement occurs. This stage is potentially reversible, since in cell culture experiments, after the exposure to a damaging factor is terminated, the podocyte shape is rapidly restored [15]. At

the second stage, the subpodocyte space disappears and podocytes closely adjoin the GBM [6]. This has been shown in experimental animal models and in HN in humans, including minimal change disease, membranous nephropathy and IgA- nephropathy [16]. At this stage, there is a complete loss of podocyte scaffolds and their fusion with the cell body, which leads to a broad disk-like podocyte proliferation, which, covering a large area of the bare GBM, prevents the protein penetration through the glomerular filter. However, the process of uplastation cannot fully prevent protein penetration through the glomerular filtration barrier; the structure and function of the slit diaphragm are altered, which eventually leads to the appearance of PU. During the process of prolapse, podocytes form long apical microvilli, a process denoted as "microvortex transformation". Microvilli have the ability to attach to the glomerular or parietal basal membrane [17]. Their appearance may indicate an attempt of the damaged podocyte to find a place of attachment to the GBM in other, less damaged areas. This mechanism is a way to protect the podocyte from its death. Podocyte pedicle proliferation and "microvillous transformation" in most cases precede partial or complete cell detachment from the GBM. One of the responses of podocytes to the action of damaging factors is hypertrophy. At the initial stage of damage, podocyte hypertrophy is of adaptive nature, there is observed activation of metabolic processes, synthesis of intracellular proteins, but without changes in podocyte function. Due to the increased size, podocytes close the nearby areas of glomerular barrier damage (compensation of cell loss) [18, 19]. But after a certain time hypertrophy becomes maladaptive, in hypertrophied cells there is a decrease in podocyte protein synthesis, cytoskeleton reorganization occurs, which promotes their detachment from GBM and development of podocyturia [18, 20]. Further effects on hypertrophied podocytes activate apoptosis processes in them. Podocytes detached from the GBM due to the disruption of cell-matrix interactions necessary to maintain their viability die, although it has been shown that some sloughed podocytes are still "viable" and can form contacts with other cells in culture [21]. Apoptosis in podocytes is activated by angiotensin II, transforming growth factor β1, active oxygen radicals, detachment from GBM, mechanical stretch, reduction of inhibitors of activated cyclic kinases p27 and p21, etc. Antiapoptotic effects are possessed by podocytic proteins (particularly nephrin), the intracellular inhibitor of apoptosis Bcl-2, preserved cell-cell contacts, and VEGF. VEGF is required for normal phosphorylation of the cleft diaphragm protein nephrin. Thus, impaired phosphorylation of nephrin in VEGF deficiency weakens nephrin binding to podocyte, leads to detachment of the extracellular part of nephrin molecule from podocyte membrane and increases its excretion with urine. Endothelial and podocyte damage with decreased expression of slit diaphragm proteins and occurrence of PU in VEGF deficiency was first shown in women with preeclampsia [22]. In an experiment, it was shown that the creation of VEGF deficiency in anti-GBM nephritis leads to a more severe course with impaired slit diaphragm

proteins, loss of podocyte stems and PU [23]. Podocyte loss is promoted by the activation of epithelial-mesenchymal transdifferentiation (EMT) mechanisms. In experiments on animal models and in epithelial cell culture, it was shown that under the influence of the main EMT inducer - transforming growth factor β1 - podocytes lose the ability to express specific podocytic proteins (nephrin, podocin, P-cadherin, ZO-1, etc.), change their epithelial phenotype and start expressing mesenchymal cell markers [24]. As a result of these processes, podocytes lose their normal cytoskeleton structure, cell polarity, intercellular contacts, and become motile, which leads to their increased sloughing from the GBM and development of podocyturia. Mechanical causes of podocyte detachment from GBM, such as intracolumnar hypertension, hyperfiltration, are also possible, leading to capillary loops stretching and increased rate of ultrafiltrate movement [25]. M. Hara et al. [26-28], using antibodies to podocytic proteins podocalyxin, podocin, nephrin, synaptopodin, identified podocytes and their fragments in the urine of patients with various glomerular diseases. The severity of podocyte excretion with urine increased in parallel with the degree of PU and reflected the activity of GN, while in healthy individuals and patients with CGN remission podocytes in the urine were determined in small amounts. Damage podocytes and the appearance of podocyturia are observed in many glomerulopathies (including focal segmental glomerulosclerosis, membranous nephropathy, mesangiocapillary HN, lupus nephritis, IgA nephropathy), correlating with disease activity. It is believed that podocyte damage in a number of forms of CGH that are not true podocytopathies may be the result of the activated renin-angiotensin-aldosterone system and a response to increased intraglomerular pressure. The role of mechanical effects on podocytes in alterations of glomerular architectonics in primary mesangial cell damage is also discussed. Thus, in Thy-1 nephritis, a change in the shape of capillary loops due to mesangial cell damage (mesangiolysis) results in protrusion of capillary loops into the urinary space. Podocytes in this case are subjected to shear stress, they are stretched, their communication with GBM is weakened, apoptosis processes are activated, thus, they become more susceptible to sloughing. The role of complement activation and membrane attack complex C5v-9 is not excluded in podocyte damage. As a result of massive podocyte damage, PU develops, which is the clinical equivalent of CGN activity. However, recent studies have shown that PU does not always fully reflect the activity of glomerular damage, while podocyturia is probably a more accurate marker of this process. Thus, in two experimental models of glomerular damage, both primary (PAN nephrosis) and secondary HN (anti-Thy1.1 nephritis), the simultaneous appearance of podocyturia and PU was found in the early stage. However, in the later stage of experimental nephritis, the disappearance of podocyturia (active damage) was noted, while PU continued to persist. The authors believe that podocyturia is a more specific indicator of active glomerular damage than PU and allows the distinction between chronic glomerular barrier defect and active

renal glomerular damage to be identified. It should be noted that in the anti-Thy1.1 nephritis model, primary damage affects the glomerular mesangial cells, but secondary damage occurs to podocytes with the development of PU. One of the stereotypic responses of podocytes to damage (exposure to hemodynamic or proinflammatory factors) is considered to be the appearance of different structural and functional proteins of podocytes and gap junction proteins (nephrin, podocin, etc.) in the urine. On the one hand, nephrin forms connections with actin fibers of the podocyte cytoskeleton, and on the other hand, nephrin molecules, interacting with each other, form an interpodocyte slit diaphragm. In the experiment, it was convincingly shown that the increased level of nephrin in the urine (nephrinuria) in NS is a consequence of damage to podocytes and the closely associated gap diaphragm, and the significance of nephrinuria as an important condition for the development of PU was demonstrated for the first time. In a study by R. Luimula et al. in a model of PAN nephrosis in rats showed increased nephrin excretion with urine at the peak of PU. In an experimental model of membranous nephropathy (Heimann's nephritis) the introduction of complement components (C5v-9) into the podocyte membrane resulted in F-actin damage and nephrin molecule detachment from the podocyte with subsequent excretion with the urine. In clinical studies, increased urinary excretion of nephrin has been found in active CGN patients [4, 8], and decreased nephrin expression in the kidney tissue of patients with PU nephropathies, regardless of their morphological form. Electron immunomicroscopy of renal tissue in patients even before the development of PU revealed areas of slit diaphragm destruction corresponding to areas of reduced nephrin expression. When the process is far advanced in the case of high PU development, the number of these areas increases significantly, and they are characterized by an irregular distribution and alternate with completely preserved areas of the slit diaphragm. Our earlier studies have shown that in CGN patients clinically presenting predominantly with PU and nephrotic syndrome, regardless of the morphological variant of nephritis, podocytes damage is revealed, accompanied by podocyturia and urinary excretion of the cleft diaphragm structural protein, nephrin. The severity of these changes depended on the level of PU, the severity of NS, and the presence of renal dysfunction. In patients with massive PU and NS, there was a decrease in the number of podocytes in renal glomeruli - podocytopenia, correlating with the value of podocyturia and the severity of renal dysfunction. In a study by Proletov et al., a decrease in PU level and nephrinuria in dynamics was observed after successful treatment of patients with cyclosporine. The influence of podocytic dysfunction on the course of CGN was clearly seen when analyzing the effect of immunosuppressive therapy: in patients with high initial level of nephrinuria and podocyturia, the response to therapy was significantly worse.

Participation of podocytes in the mechanisms of nephrosclerosis formation

Experimental and clinical evidence has accumulated that the number of podocytes in the glomerulus is an important determinant of the development of glomerulosclerosis; progressive forms of CGN are shown to be accompanied by podocytopenia. Under conditions of normal kidney tissue development, a large number of nephrons are laid down, which exceeds the number sufficient for kidney function. This contributes to the adaptation of the kidney to the increasing demands in the growing body and in adults. After 60 years of age, the number of nephrons decreases by 50%, in which case the initial oligonephronia is one of the leading causes of renal failure formation in kidney disease. But even with a normal number of nephrons at birth, the loss of podocytes in primary and secondary glomerulopathies is important in the development of renal failure. The total number of podocytes in the glomerulus is determined by the balance of their proliferation and loss processes. Mature podocytes are highly differentiated cells, practically not dividing, with low proliferative potential. At present, thanks to the achievements of experimental nephrology and modern cell technologies, it has been convincingly shown that podocyte loss can be partially compensated by podocyte progenitor stem cells that are localized at the urinary pole of the glomerulus in the area of the connection of the glomerular and tubular epithelium and along the bowmen capsule. Progenitor cells can migrate to the denuded areas of the GBM, which has been shown in some experimental models of CGN. It has also been found that the parietal epithelial cells of the Bowman capsule express the stem cell markers CD24 and CD133. As they approach the vascular pole of the glomerulus, they gradually lose these markers, acquire podocytic markers, and differentiate into mature podocytes. Presumably, another source of podocyte renewal in the glomerulus may be bone marrow stem cells. However, there are no works confirming this assumption under clinical conditions in humans. There is also no data on the fact that in the human glomerulus there are conditions for programmed migration of progenitor cells in "denuded" areas of the GBM in the normal or in the loss of podocytes. Finally, the constant movement of ultrafiltrate in the bowmen's space also prevents the attachment and division of these cells. Thus, podocytes as highly differentiated cells are incapable of proliferation and replacement, so the progressive loss of these cells in the glomerulus of the kidney leads to the denudation of the SBM and triggers the processes of glomerulosclerosis [1]. An important mechanism of podocyte loss is the activation of apoptosis process that promotes podocyte detachment from the GBM and excretion into the urinary space. The processes of maladaptive podocyte hypertrophy and EMT, which reduce cell adhesive properties and promote podocyte sloughing, are also discussed. Thus, in cell culture it has been shown that podocyte response to mechanical stretch is hypertrophy, in particular, due to activation of cell cycle inhibitors. In this case, nucleus division is quite often observed, while complete cell division does not occur, which is proved by the appearance of binuclear and multinucleated podocytes. Parallel to podocyte hypertrophy, there is a decrease in

adhesive properties of the cells, their separation from GBM and sloughing into the urine. Podocyte loss is promoted by the activation of epithelial-mesenchymal transdifferentiation mechanisms. During EMT, podocyte dedifferentiation and acquisition of mesenchymal cell markers, including expression of matrix metalloproteinases (MMPs), MMP-2 and MMP-9 localize in EMT areas, inducing the appearance of myofibroblasts. Increased MMP expression stimulates GBM destruction as well as migration of cells transformed into myofibroblasts. Similar to fibroblasts, transdifferentiated podocytes acquireability to produce matrix proteins (fibronectin, collagen, etc.), thus accelerating the formation of glomerulosclerosis. Reducing the number of podocytes leads to "denudation" of some areas of GBM, loss of shape of capillary loops with the formation of local bulges of basal membrane. When these "bulges" come in contact with glomerular parietal cells, synechiae between capillary loops and glomerulus bowmen capsule are formed, which is the trigger mechanism for the beginning of glomerular sclerosing [65]. It has been shown that loss of podocytes in glomerulus up to 20% is accompanied by mesangial expansion, 20-40% - by formation of synechiae with capsule, at loss of 40-60% podocytes glomerulosclerosis develops, marked depletion of podocytes >60% leads to global glomerulosclerosis. Critical reduction in the number of podocytes in the glomeruli is a major factor in the progression of glomerulosclerosis and decreased glomerular filtration rate.

Prospects for noninvasive assessment of podocytic damage

Given the important role of podocyte damage in the development of PU and progression of glomerulosclerosis, in recent years there has been a significant increase in interest in "urinary" biomarkers, quantitative determination of which allows non-invasive monitoring of the severity of structural and functional disorders of podocytes. To determine the severity of glomerular filter damage in patients with various forms of GN, different methods are currently used - creation of cell culture to determine "viable" podocytes and podocytes in the state of apoptosis in urine, evaluation by immunoenzymatic method of the level of structural proteins of podocytes and slit diaphragm (nephrin, podocyn, synaptopodin, podocalixin and others).), cytofluometry in urine sediment of antibody-labeled podocytes to podocalyxin, as well as urine immunoblotting to detect mRNA of these proteins. In recent years, there is evidence that most immunosuppressive drugs used in the treatment of GN, in addition to the systemic action, have an effect directly on the podocyte, this mechanism is the determinant in the reduction of PU and HC termination [29]. Thus, a promising direction is the development of targeted drugs aimed at restoring the structure and function of the podocyte.

Conclusion

Thus, structural and functional disorders of podocytes (podocytopathy), previously considered a specific feature of minimal change disease, membranous nephropathy and focal

segmental glomerulosclerosis, are found in different variants of CGN occurring with PU and NS. Despite the fact that the proteinuric forms of glomerular renal lesions differ in etiology, pathogenesis and clinical course, they are united by a common phenotype of podocyte damage: changes in the structure and apical displacement of the interpodocyte cleft diaphragm, reorganization of the actin cytoskeleton of podocytes with the development of a smoothing effect of the stalk processes, detachment of podocytes from the GBM with their appearance in the urine (podocyturia) and subsequent decrease in their number in the glomerulus (podocytopenia). Changes in podocytes associated with immune and hemodynamic disorders in CGN may precede the development of large PU, and their increase is closely associated with morphological and clinical manifestations of CGN progression. Currently, available methods for noninvasive assessment of podocytic damage using urinary tests have emerged. Determination of podocyturia and the level of urinary excretion of podocytic proteins (nephrin, podocin, etc.) seem promising to determine the severity of glomerular damage, assess the risk of glomerulosclerosis and predict the effectiveness of CGN therapy.

LITERATURE

1. Жуманазаров, С. Б., Жаббаров, А. А., Мирзаева, Г. П., Эшонов, Ш. Н., & Бобокулов, М. Б. (2021). Прогностическое Значение Клинико-Патогенетических Особенностей Развития Хронической Болезни Почек Вследствие Гломерулярных Заболеваний. CENTRAL ASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES, 2(2), 175-184.
2. Низамова, Н. Г., Максудова, М. Х., & Жуманазаров, С. Б. (2021). ИЗУЧЕНИЕ ЗАВИСИМОСТИ ПРИОБРЕТЕННЫХ ПОРОКОВ СЕРДЦА ОТ СТЕПЕНИ ПОРАЖЕНИЯ КЛАПАНА У ПАЦИЕНТОВ С ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ. Моя профессиональная карьера, 1(24), 7-19.
3. ЙУЛДОШеВ, Т. Р., ЖАББАРОВ, О., МАКСУДОВА, М., & ЖУМАНАЗАРОВ, С. ОЦЕНКА ПОРАЖЕНИЯ ЖЕЛУДОЧНО-КИШЕЧНОГО ТРАКТА У БОЛЬНЫХ ХРОНИЧЕСКОЙ БОЛЕЗНЬЮ ПОЧЕК III–IV СТАДИИ И ПУТИ ИХ КОРРЕКЦИИ. AXBOROTNOMASI, 95.
4. Аляви, А. Л., Турсунова, Л. Д., Бувамухамедова, Н. Т., & Жуманазаров, С. Б. (2021). ТЕЧЕНИЕ СЕРДЕЧНО-СОСУДИСТЫХ ЗАБОЛЕВАНИЙ У БОЛЬНЫХ COVID-19. Студенческий вестник, (17-4), 38-41.
5. Жуманазаров, С. Б., Жаббаров, А. А., Султонов, Н. Н., & Арипова, Н. А. СРАВНИТЕЛЬНАЯ ЭФФЕКТИВНОСТЬ ПРИМЕНЕНИЯ ПРЕПАРАТА ЭРИТРОПОЕТИНА И ПРЕПАРАТА ЖЕЛЕЗА У БОЛНЫХ ХПБ III И IVСТАДИИ. *VIII МЕЖДУНАРОДНОГО КОНГРЕССА «КАРДИОЛОГИЯ НА ПЕРЕКРЕСТКЕ НАУК»*, 103.
6. Жуманазаров, С. Б., Кадырова, Ш. А., & Нишонова, Ю. У. ОСОБЕННОСТИ ТЕЧЕНИЯ ИШЕМИЧЕСКОЙ БОЛЕЗНИ СЕРДЦА У ПОЖИЛЫХ. *СБОРНИК ТЕЗИСОВ*, 80.

7. Қодирова, Ш., Жуманазаров, С., & Сапаева, З. (2021). ПОДАГРАДА БУЙРАКЛАР ЗАРАРЛАНИШИНИНГ КЛИНИК ХУСУСИЯТЛАРИ.

8. Jumanazarov, S. B., Jabbarov, O. O., Sapaeva, Z. A., Farmonov, A. S., & Buvamuxamedova, N. T. (2021). The role of genetic factors in the development of chronic glomerulonephritis. *Journal For Innovative Development in Pharmaceutical and Technical Science (JIDPTS)*, *4*(04).

9. Косимбаев, С., Аляви, А., Турсунова, Л., & Жуманазаров, С. (2021). АГРЕГАТНОЕ СОСТОЯНИЕ КРОВИ И КОАГУЛЯЦИОННЫЙ ГЕМОСТАЗ У БОЛЬНЫХ С ИШЕМИЧЕСКИЙ БОЛЕЗНЬЮ СЕРДЦА ПЕРЕНЕСШИХ COVID-19.

10. Эшметова, С., Кенжаев, М., Максудова, М., & Жуманазаров, С. (2021). ВОЗНИКНОВЕНИЕ ЖЭЛУДОЧКОВАЯ АРИТМИЙ СЕРДЦА У БОЛЬНЫХ ПОСТИНФАРКТНЫМ КАРДИОСКЛЕРОЗОМ И МЕТОДЫ ИХ ЛЕЧЕНИЯ.

11. Greka A, Mundel P. Cell biology and pathology of podocytes. Ann Rev Physiol. 2012;74:299-323. doi: 10.1146/annurev-physiol-020911-153238

12. Couser W.G. Basic and translational concepts of immune - mediated glomerular diseases. J Am Soc Nephrol. 2012;23:381-99. doi: 10.1681/ ASN.2011030304.

13. Jefferson J.A, Shankland S.J, Pichler R.H. Proteinuria in diabetic kidney disease: A mechanistic viewpoint. Kidney Int. 2008;74:22-36. doi: 10.1038/ki.2008.128

14. George B, Verma R, Soofi A, Garg P, Zhang J, Park T.J, Giardino L, Ryzhova L, Johnstone D, Wong H, Nihalani D, Salant D, Hanks S, Curran T, Rastaldi M, Holzman L. Crk1/2-dependent signaling is necessary for podocyte foot process spreading in mouse models of glomerular disease. J Clin Invest. 2012;122:674- 92. doi: 10.1172/ JCI60070

15. Reiser J, von Gersdorff G, Loos M, Oh J, Asanuma K, Giardino L, Rastaldi M, Calvaresi N, Watanabe H, Schwarz K, Faul C, Kretzler M, Davidson A, Sugimoto H, Kalluri R, Sharpe A, Kreidberg J, Mundel P. Induction of B7-1 in podocytes is associated with nephrotic syndrome. J Clin Invest. 2004;113:1390- 7. doi: 10.1172/JCI20402

16. Shirato I. Podocyte process effacement in vivo. Micros Res Tech. 2002;57:241-6. doi: 10.1002/jemt.10082

17. Le Hir M, Keller C, Eschmann V, Hähnel B, Hosser H, Kriz W. Podocyte bridges between the tuft and Bowman's capsule: an early event in experimental crescentic glomerulonephritis. J Am Soc Nephrol. 2001;12:2060-71.

18. Nagata M. Podocyte injury and its consequences. Kidney Int. 2016 Jun; 89(6):1221-30. doi: 10.1016/j.kint.2016.01.012

19. Neal C, Crook H, Bell E, Harper S, Bates D. Three-dimensional reconstruction of glomeruli by electron microscopy reveals a distinct restrictive urinary subpodocyte space. J Am Soc Nephrol. 2005;16:1223-35. doi: 10.1681/ASN.2004100822

20. Liapis H, Romagnani P, Anders H.J. New insights into the pathology of podocyte loss: mitotic catastrophe. Am J Pathol. 2013;183:1364-74. doi: 10.1016/j.ajpath.2013.06.033

21. Vogelmann S.U, Nelson W.J, Myers B.D, Lemley K.V. Urinary excretion of viable podocytes in health and renal disease. Am J Physiol Renal Physiol. 2003;285(1):40-8. doi: 10.1152/ajprenal.00404.2002.

22. Garovic V.D, Wagner S.J, Petrovic L.M, Gray C.E, Hall P, Sugimoto H, Kalluri R, Grande J.P. Glomerular expression of nephrin and synaptopodin but not podocin is decreased in kidney sections from women with preeclampsia. Nephrol Dial Transplant. 2007;22:1136-43. doi: 10.1093/ndt/gfl711

23. Hara A, Wada T, Furuchi K, Sakai N, Kawachi H, Shimizu F, Shibuya M, Matsushima K, Yokoyama H, Egashira K, Kaneko S. Blokade of VEGF accelerates proteinuria via decrease in nephrin expression in rat crescentic glomerulonephritis. Kidney Int. 2006;69(11):1986-95. doi: 10.1038/sj.ki.5000439

24. Liu Y. New insights into epithelial - mesenchymal transit contribute in kidney fibrosis. J Am Soc Nephrol. 2010;21:212-22. doi: 10.1681/ASN.2008121226

25. Kriz W, Lemley K. A potential role for mechanical forces in the detachment of podocytes and the progression of CKD. J Am Soc Nephrol. 2015;26:258-69. doi: 10.1681/ASN.2014030278

26. Hara M, Yanagihara T, Kihara I. Urinary podocytes in primary focal segmental glomerulosclerosis. Nephron. 2001;89:342-7. doi: 10.1159/ 000046097

27. Hara M, Yanagihara T, Kihara I, Higashi K, Fujimoto K, Kajita T. Apical cell membranes are shed into urine from injured podocytes: A novel phenomenon of podocyte injury. J Am Soc Nephrol. 2005;16:408-16. doi: 10.1681/ASN.2004070564.

28. Hara M, Yanagihara T, Kihara I. Cumulative excretion of urinary podocytes reflects disease progression in IgA nephropathy and Schönlein-Henoch purpura nephritis. Clin J Am Soc Nephrol. 2007;2:231-8. doi: 10.2215/CJN.01470506.

29. Müller-Deile J, Schiffer M. Podocytes from the diagnostic and therapeutic point of view. Pflugers Arch. 2017;469(7-8):1007-15. doi: 10.1007/s00424-017- 1993-z.