ISSN 1607-419X
ISSN 2411-8524 (Online)
УДК 616.61:616.12

Molecular and cellular mechanisms and mediator system of kidney and heart remodeling in chronic kidney disease — the target of nephro- and cardioprotection

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Received 10 October 2014; accepted 30 October 2014.

Abstract

The lecture reviews molecular and cellular mechanisms, which are cornerstone of structural and functional remodeling and kidney and heart fibrosis formation in chronic kidney disease. The key ways linking kidney and heart remodeling, including myofibroblast formation by epithelial-mesenchymal and endotelial-mesenchymal transdifferentiation, extracellular matrix production, are presented. The role of angiotensin II, transforming growth factor ß1, plasminogen activator inhibitor type I, vascular endothelial growth factor, matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases in mechanisms of fibro- and angiofibrogenesis are discussed. Further research of the molecular and cellular mechanisms of tissue fibrosis broadens our understanding about nephro- and cardioprotective effects of traditional approaches (angiotensin converting enzyme inhibitors or angiotensin II receptor blockers) and gives an opportunity for therapy targeting common mediators of fibro- and angiofibrogenesis in kidneys and heart.

Key words: renal and cardiac remodeling, epithelial-mesenchymal transdifferentiation, endothelial-mesenchymal transdifferentiation, myofibroblasts, angiotensin II, mediators of fibrosis, cardio-nephroprotection

For citation: Bobkova IN, Kozlovskaya LV, Nanchikeeva ML, Chebotareva NV, Li AO. Molecular and cellular mechanisms and mediators system of kidney and heart remodellings in chronic kidney disease — the target of nephro- and cardioprotection. Arterial Hypertension = Arterial'naya Gipertenziya. 2014;20(6):492–500.

Молекулярно-клеточные механизмы и система медиаторов ремоделирования почек и сердца при хронической болезни почек — мишень нефрокардиопротекции

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Статья поступила в редакцию 10.10.14 и принята к печати 30.10.14.

Резюме

В лекции рассмотрен ряд молекулярно-клеточных механизмов, лежащих в основе структурно-функциональной перестройки и формирования фиброза в почках и сердце при хронической болезни почек. Авторами подробно освещено ключевое звено дезадаптивного ремоделирования органов — образование миофибробластов путем эпителиально-мезенхимальной и эндотелиально-мезенхимальной трансдифференциации, роль в регуляции данных процессов ведущих медиаторов ангиофиброгенеза (ангиотензина II, трансформирующего фактора роста ß1, ингибитора активатора плазминогена I типа, сосудистого эндотелиального фактора роста, матриксных металлопротеиназ и их ингибиторов и других). Изучение молекулярно-клеточных основ органного фиброза, в том числе факторов дисрегуляторной активации, дифференциации и выживаемости миофибробластов, позволяет уточнить механизмы действия традиционных средств нефро- и кардиопротекции, а также открывает возможность целенаправленного (таргетного) влияния на отдельные звенья фиброгенеза и расширяет арсенал средств, тормозящих ремоделирование в почках и сердце.

Ключевые слова: ремоделирование почек и сердца, эпителиально-мезенхимальная трансдифференциация, эндотелиально-мезенхимальная трансдифференциация, миофибробласты, ангиотензин II, медиаторы фиброза, нефрокардиопротекция

Для цитирования: Бобкова И. Н., Козловская Л. В., Нанчикеева М. Л., Чеботарёва Н. В., Ли О. А. Молекулярно-клеточные механизмы и система медиаторов ремоделирования почек и сердца при хронической болезни почек — мишень нефрокардиопротекции. Артериальная гипертензия. 2014;20(6):492–500.

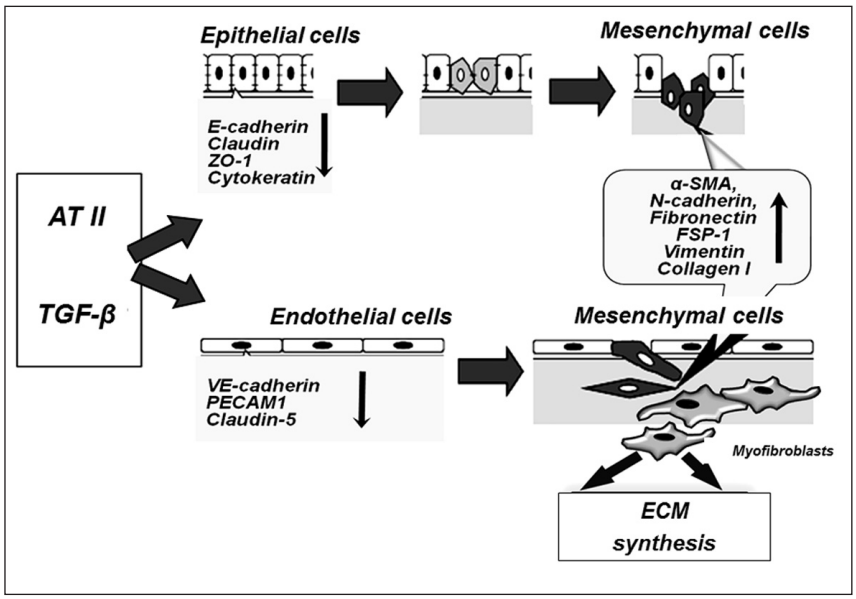
Based on the long-term experience in chronic kidney disease (CKD), medications inhibiting angiotensin II (AT-II) effects are believed to have both nephro- and cardioprotective effects, which led to a concept of reciprocal connection between kidneys and heart (inter-organ «cross-talk»). On the other hand, it stimulated further research of shared mechanisms, including molecular and cellular interactions (intraorgan "cross-talk"), leading to structural and functional remodeling of kidneys and heart. This is promising for the development of new nephroprotective treatment approaches in CKD.

According to modern concepts, the formation of myofibroblasts (MFB) from resident fibroblasts and by epithelial-mesenchymal transdifferentiation (EMT) and endothelium-mesenchymal transdifferentiation (EndMT) is one of the most important aspects of maladaptive remodeling (primarily, fibrosis development) [1 –3]. In the course of transdifferentiation, cytoskeleton of the mature epithelial and endothelial cells changes, they lose their inherent biomarkers and acquire mesenchymal phenotype. So, they express smooth muscle alpha-actin (alpha-SMA), fibroblast-specific protein (FSP-1), fibronectin, collagen type I, vimentin and other markers. At the same time the synthesis of extracellular matrix (ECM) increases and organ fibrosis develops (Fig. 1). Being a key mediator of fibrogenesis and angiofibrogenesis, AT-II plays the major role in the regulation of these molecular-cellular interactions. AT-II acts directly or via secretion of transforming growth factor β1 (TGF-β1) by monocytes and fibroblasts (there are angiotensin receptros on the surface of these cells), or through the interaction with mediators of fibrinolysis / proteolysis, e. g. activator inhibitor plasminogen type I (PAI–I) [4–6].

In heart MFB are generated not only fromresident fibroblasts (from fetal propicardial pool) and bone marrow cells (monocytes and fibroblasts), but also from pericytes and endothelial microvascular cells. Their EMT and EndMT are mediate by fibrogenic signals, including AT-II [7–9] (Fig. 2).

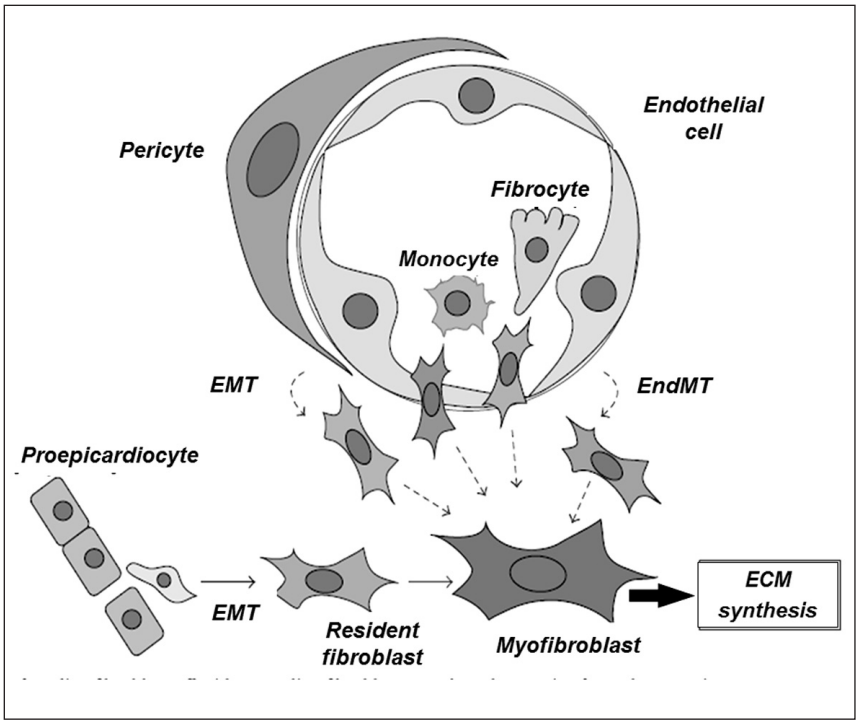
In case of renal damage, highly and completely differentiated glomerular podocytes can undergo EMT [10, 11]. They lose their specific markers, acquire characteristics of mesenchymal precursors, which leads to their dysfunction (Fig. 3). Podocytes become mobile and separate out of the glomerular basal membrane and are washed away with urine (podocyteuria). Increased podocyteuria is associated with podocytopenia, which is considered an important factor for glomerulosclerosis development [12, 13]. Epithelial tubular cells can also transform into renal interstitial MFB (Fig. 3). Under the influence of damaging factors (components of proteinuria, reactive

Figure 1. Mesenchymal transdifferentiation of epithelial and endothelial cells



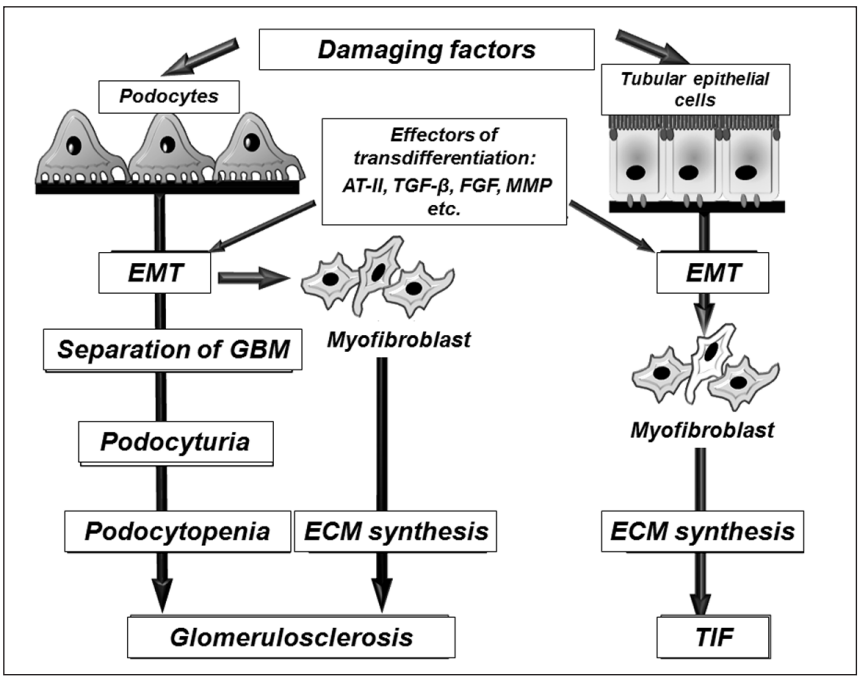
Note: AT-II — angiotensin II; TGF-β — transforming growth factor β; ECM — extracellular matrix; VE-cadherin — vascular endothelial cadherin; PECAM1 — endothelial and platelet adhesion molecule 1.

Figure 2. The origin of cardiac myofibroblasts



Note: EMT — epithelial mesenchymal transdifferentiation; EndMT —endothelial mesenchymal transdifferentiation; ECM — extracellular matrix.

Figure 3. The formation of myofibroblasts in the kidney



Note: AT-II — angiotensin II; TGF-β1 — transforming growth factor β1; FGF — fibroblast growth factor; MMPs — matrix metalloproteinases; EMT — epithelial mesenchymal transdifferentiation; GBM — glomerular basement membrane; ECM — extracellular matrix; TIF — tubulointerstitial fibrosis.

Table 1

URINARY BIOMARKERS OF ANGIOFIBROGENESIS AND ENDOTHELIAL DYSFUNCTION IN HYPERTENSIVE PATIENTS DEPENDING ON THE PRESENCE OF MICROALBUMINURIA

Parameter	n	HTN without MAU	n	HTN with MAU	p
PAI-1, ug/ml	11	0.147 [0.130; 0.161]	42	0.184 [0.165; 0.197]	p = 0.002
TGF-β1, pg/ml	17	0.21 [0.193; 0.237]	53	0.29 [0.244; 0.306]	p = 0.0002
VEGF, pg/ml	17	69.7 [64.1; 78.42]	54	83.4 [73.15; 90.73]	p = 0.005
Type IV collagen, ng/ml	10	3.07 [2.11; 4.91]	26	10.3 [5.36; 17.52]	p = 0.008

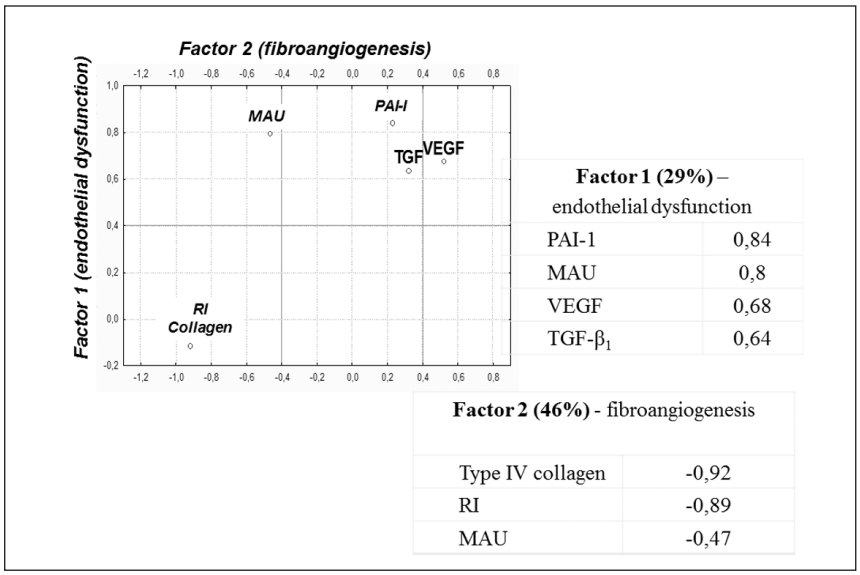
Note: The variables are presented as the median and interquartile range [25-75%]; HTN — hypertension; MAU — microalbuminuria; PAI-1 — plasminogen activator inhibitor type I; TGF-β1 — transforming growth factor β1; VEGF — vascular endothelial growth factor.

oxygen species, complement proteins and other), tubular epithelial cells transdifferentiate into MFB, migrate into the interstitial tissue, and participate in the production of ECM components and formation of renal tubulointerstitial fibrosis (TIF) [14, 15]. The role of EMT mechanisms in the TIF development and progression of CKD was confirmed by many studies, including ours [16, 17].

Thus, the role of the conversion of endothelial and epithelial cells in MFB in the genesis of renal and cardiac fibrosis is undoubtful and the mechanisms of EMT EndMT require further investigation. A number of mediators (extra- and intracellular) controlling EMT and EndMT were identified in experimental studies [2, 4, 6].

Previously we studied some urinary biomarkers of renal angiofibrogenesis in essential hypertension (HTN). We demonstrated that hypertensive nephropathy (HNP) is a dynamic process with stage-specific clinical, functional and urinary biomarkers. In 40 % of patients, renal damage, along with cardiovascular involvement, develops within within 5 years from HTN onset. According

Figure 4. The multivariate analysis of the association between molecular markers in patients with essential hypertension



Note: MAU — microalbuminuria; PAI-I — plasminogen activator inhibitor type I; RI — resistance index; VEGF — vascular endothelial growth factor; TGF-β1 — transforming growth factor β1.

to our data, albuminuria is found at early stage of HNP, and its frequency and severity correlate with HTN severity and population risk factors. Later, intrarenal vascular resistance increases (it can be estimated by resistance index (RI) of interlobar arteries by Doppler), and the glomerular filtration rate gradually decreases after a long-lasting hyperfiltration phase without hypercreatininemia [18, 19].

Hypertensive patients with albuminuria have significantly higher urinary excretion of the mediators — plasminogen activator inhibitor type 1 (PAI-1), vascular endothelial growth factor (VEGF), TGF-β1 and collagen type IV. This reflects endothelial dysfunction and related mechanisms of angiofibrogenesis that is the pathophysiological basis for renal microvascular remodeling (Table 1).

There is a "cross-talk" between all the components of this complex regulatory system. The multivariate analysis identified two factors that cluster 75% of the studied parameters in hypertensive patients (Fig. 4).

Factor 1 (29% of the parameter dispersion) unites albuminueria, PAI-1, TGF-β1 and VEGF. It confirms the role of local renal endothelial dysfunction in the HNP development, being adaptive at initial stages in order to preserve autoregulation mechanisms of intrarenal flow. Factor 2 (46% of the dispersion), grouped together albuminuria, RI and urinary excretion of collagen type IV. It seems to reflect the next stage with the maladaptive renal microvascular remodeling, enhanced ischemia and renal tissue hypoperfusion.

The levels of PAI-1, VEGF, TGF-β1 thickness correlated with left ventricular posterior wall ($R = 0.30$, $p < 0.05$; $R = 0.42$, $p < 0.05$ and $R = 0.37$, $p < 0.005$, respectively), and the level of urinary TGF-β1 correlated with the thickness of "intima-media" complex of the common carotid artery ($R = 0.28$, $p < 0.05$). These associations confirm the role of urinary biomarkers in kidney and heart remodeling as the part of renocardiovascular continuum. On the other hand, taken into account renocardiovascular interrelat ion and a major role of angiotensin II in EMT and EndMT, its inhibitors appear to be highly relevant in hypertension due to their nephron- and cardioprotective effects. To test this hypothesis, we analyzed the effects of renin-angiotensin system blockade in a group of 72 patients who

Table 2

URINARY EXCRETION OF ANGIOFIBROGENESIS MARKERS AND EXTRACELLULAR MATRIX COMPONENTS IN PATIENTS WITH CHRONIC GLOMERULONEPHRITIS

Parameter	CGN without NS (I)	CGN with NS without renal failure (II)	CGN with NS and renal failure (III)	p < 0.05
TGF-β1, pg/ml n = 63	n = 23 1.65 [0,7–2,2]	n = 29 1.1 [0.4–2.4]	n = 11 3.0* [2.2–4.6]	* — compared to I and II
VEGF, pg/ml n = 67	n = 19 71.2 [55.8–88.2]	n = 37 125.2 ° [94.6–179.7]	n = 11 54.65* [38.7–71.5]	* — compared to I and II ° — compared to I
Type IV collagen, ng/ml n = 44	n = 16 7.5 [5.11–11.1]	n = 10 15.0° [7.55–17.25]	n = 18 35.2* [60.05–20.25]	* — compared to I and II ° — compared to I
Fibronectin, ug/ml n = 67	n = 19 6.0 [7.11–10.1]	n = 37 15.0° [15.0–20.0]	n = 11 30.0* [30.0–20.0]	* — compared to I and II ° — compared to I

Note: The variables are presented as the median and interquartile range [25-75%]; CGN — chronic glomerulonephritis; NS — nephrotic syndrome; TGF-β1 — transforming growth factor β1; VEGF — vascular endothelial growth factor.

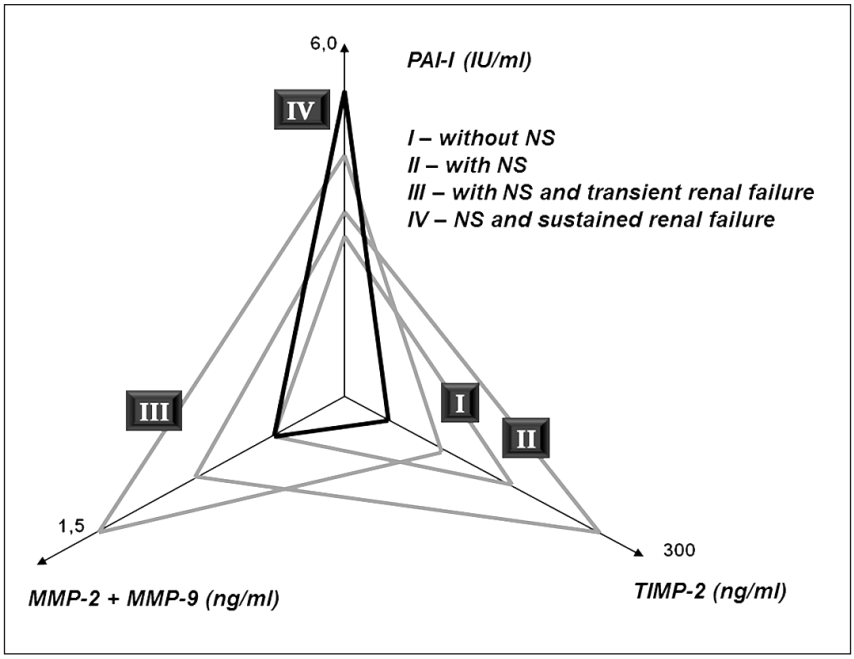
got angiotensin-converting enzyme (ACE) inhibitors in addition to lifestyle and risk factor modification [20]. All the patients have received angiotensin-converting enzyme (ACE) inhibitors (renitek or fosinopril) in average therapeutic doses for at least 6 months. Blood pressure (BP) decreased below < 140/90 mm Hg in in 41 (55 %) subjects, while target BP was not achieved in 31 (45 %) patients, despite significant reduction in systolic and diastolic BP by the end of 6-month therapy. A significant decrease in albuminuria and its complete disappearance was found in more than half (28 out of 41 patients, 68 %) of the subjects. Twenty-eight patients with normalized levels of albuminuria demonstrated a decrease of initially high RI, 8 of them had a positive dynamics of heart remodeling at echocardiography [20].

In addition, we assessed the mentioned urinary biomarkers (EMT regulators) and their expression in renal tissue in patients with chronic glomerulonephritis (CGN), those with significant proteinuria without nephrotic syndrome (NS), with NS and preserved renal function, and with NS and renal failure (RF), as a manifestation of the high-active nephritis (Table 2).

Thus, urinary excretion of the main EMT inductor TGF-β1 was the highest in patients with NS and RF (Table 2), and it directly correlated with the serum creatinine level ($R = 0.51$, $p < 0.05$) and the area of TIF estimated by morphometrical methods ($R = 0.51$, $p < 0.05$) [17, 21]. These patients also showed the highest expression of TGF-β1 in renal tissue (especially in tubulointerstitium) and an intense expression of the mesenchymal MFB marker α-SMA by the tubular epithelial cells, which was defined by immunohistochemistry peroxidase method [21, 22].

Patients with CGN and nephrotic syndrome had significantly higher VEGF excretion patients with less severe proteinuria. VEGF determines proliferative and regenerative properties of endothelium and affects the intensity of apoptosis of the endothelial cells and their integrative properties (Table 2). Urinary VEGF index directly correlated with the level of proteinuria ($Rs = 0.67$, $p < 0.0001$) in patients with preserved renal function. Patients with CGN and renal failure VEGF was reduced (Table 2). In patients with CGN and verified TIF, its urinary excretion was significantly lower than in patients without tubulointerstitial alterations. Our results are consistent with the data that chronic

Figure 5. Urinary excretion of matrix proteinases and their inhibitors in patients with chronic glomerulonephritis



Note: PAI-I — plasminogen activator inhibitor type I; MMPs — matrix metalloproteinases; TIMP — tissue inhibitor of matrix metalloproteinase; NS — nephrotic syndrome.

sclerotic stage of CKD is associated with the disruption of vascular homeostasis, decreased secretion of VEGF, which leads to the disintegration of the monolayer of vascular endothelial cells. The latter ones do not produce VEGF, but are regulated by an outer factor in a dose-dependent manner [23, 24]. Patients with CGN, TIF and renal failure demonstrated a strong relation between urine VEGF decline and increased urine TGF-β1 level ($R = –0.623$, $p < 0.05$).This indicates a "cross talk" between the regulatory factors of EMT and EndMT, and it is mediated by paracrine mechanisms. The highest level of urinary excretion of ECM components, type IV collagen and fibronectin, reflects the severity of renal fibrosis (glomerular, interstitial) in patients with CGN, nephrotic syndrome and renal failure (Table 2). We also assessed urinary excretion of proteolysis system components, such as matrix metalloproteinases (MMP-2 and MMP-9) and their inhibitor (tissue inhibitor of MMP, TIMP-2) and PAI-1, in patients with CGN [25, 26]. The MMPs are active regulators of the accumulation of ECM components, and are involved in EMT mechanisms leading to organ fibrosis [27]. Thus, the higher activity of the disease (increase in proteinuria, nephrotic syndrome, a transient impairment of renal function) is associated with the concordant changes in all the factors — an increase in urine levels of MMP, TIMP and PAI–I (Fig. 5). These changes are supposed to be adaptive in nature when associated with the active inflammation in the kidney and increased accumulation of ECM.

Patients with persistent Mo demonstrated an imbalance in the proteolysis system characterized by an abrupt decline in urinary MMP-2, MMP-9, and TIMP-2 and a disproportionately high activity of PAI-1 (Fig. 4). N our opinion, these alterations reflect maladaptive renal remodeling and can be considered a marker of poor prognosis, indicating a high risk of TIF development and renal failure progression.

We believe that the level of urinary excretion of ECM components fibronectin and type IV collagen is an integrative marker of maladaptive renal remodeling. Their urine level significantly increased in patients with CGN, renal failure and verified glomerulosclerosis (Table 2) and correlated with serum creatinine level ($Rs = 0.70$, $p < 0.001$ — for fibronectin, and $Rs = 0.48$, $p < 0.005$ for collagen). Therefore, they can be used for the noninvasive evaluation of renal fibrosis in clinical practice.

Experimental studies showed that angiotensin II plays a key role at all stages of the development of renal fibrosis mediated by TGF-β1 and PAI–I [28, 29]. We assessed the effect of angiotensin receptor blocker II (ARB) valsartan on renal remodeling in patients with active forms of CGN. Thirty-seven patients with CGN took valsartan as monotherapy, among them 16 did not have nephrotic syndrome, 10 subjects had nephrotic syndrome, and 11 patients had nephrotic syndrome and moderate renal failure. Besides antihypertensive and antiproteinuric effects, three-months valsartan monotherapy in a therapeutic dose, was associated with significant decrease in molecular mediators of fibrogenesis, in particular, with the reduction in urine level of PAI–I and fibronectin, in all groups of patients with CGN [22]. Thus, the anti-fibrotic effects of some conventional drugs with nephro- and cardioprotective properties, including ACE inhibitors and ARBs mediated by the suppression of EMT and EndMT. Molecular and cellular mechanisms of organ fibrosis, including mediators of disregulatory activation, differentiation and survival of MFB requires further elucidation and presents promising new approaches for nephron-and cardioprotection in patients with CKD.

Conflict of interest

The authors declare no conflict of interest.

References

1. Kalluri R, Neilson EG. Epithelial-mesenchymal transitition and its implication for fibrosis. J Clin Invest. 2003;112(12):1776–1784.

2. Yoshimatsu Y, Watabe T. Role of TGF-β1 signals in endothelial-mesenchymal transitition in cardiac fibrosis. International Journal of Inflammation. 2011;2011:724080–724087.

3. Zeisberg M, Neilson EG. Biomarkers for epithelial-to-mesenchymal transitition. J Clin Invest. 2009;119 (6):1429–1437.

4. Leask A. Potential therapeutic targets for cardiac fibrosis: TGF-β, angiotensin, endothelin, CCN2 and PDGF? Partners of fibroblast activation. Circulation Research. 2010;106(11):1675–1680.

5. Liu Y. Epithelial to mesenchymal transition in renal fibrogenesis: pathologic significance, molecular mechanism, and therapeutic intervention. J Am Soc Nephrol. 2004;15:1–12.

6. Eddy AA, Fogo AB. Plasminogen activator inhibitor-1in chronic kidney disease: evidence and mechanisms of action. J Am Soc Nephrol. 2006;17(11):2999–3012.

7. Takeda N, Manabe I. Cellular interplay between cardiomyocytes and nonmyocytes in cardiac remodeling. International Journal of Inflammation. 2011;2011:535241–535253.

8. Porter KE, Turner NA. Cardiac fibroblasts: at the heart of myocardial remodeling. Pharmacology and Therapeutic. 2009;123:255–278.

9. Zeisberg EM, Tarnavski O, Zeisberg M, Dorfman AL, McMullen JR, Gustafsson E et al. Endothelial-to-mesenchymal transitition contributes to cardiac fibrosis. Nature Medicine. 2007;13(8):952–961.

10. Liu Y. New insights into epithelial-mesenchymal transitition contribute in kidney fibrosis. J Am Soc Nephrol. 2010;21:212–222.

11. Zeisberg EM, Kalluri R. Epithelial-to-mesenchymal transitition contributes in renal fibrosis. Journal of molecular medicine. 2004;82(3):175–181.

12. Kriz W, Greitz N, Lemley KV. Progression of glomerular diseases: is the podocyte the culprit? Kidney Int. 1998;54(3):687–697.

13. Lemley KV, Lafayette A, Safai G, Derby G, Blouch K, Squarer A et al. Podocytopenia and disease severity in IgA nephropathy. Kidney Int. 2002;61(4):1475–1485.

14. Galichon P, Hertig A. Epithelial to mesenchymal transitition a biomarker in renal fibrosis: are we ready for bedside? Fibrogenesis and Tissue repair. 2011;4:11–17.

15. Kriz W, Kaissling B, Le Hir M. Epithelial-mesenchymal transitition in kidney fibrosis: fact or fantasy? J Clin Invest. 2011;121:468–472.

16. Muckhin NA, Kozlovskaya LV, Bobkova IN, Plieva OK, Chebotareva NV, Scherbak AV. Renal tubulointerstitium remodeling induced by proteinuria and nephroprotection in chronic glomerulonephritis. Vestnik RAMN. 2005;1:3–8. In Russian.

17. Kozlovskaya LV, Bobkova IN, Plieva OK, Chebotareva NV, Scherbak AV, Muckhin NA. Significance of research in urine of molecular mediators of renal immune inflammation and fibrosis in chronic glomerulonephritis. Terapevticheskiy arkhiv. 2004;9:84–87. In Russian.

18. Nanchikeeva ML, Konechnaya EY, Bulanov MN, Gladkaya AA. Possibilities of early diagnostics of kidney damage in patients with arterial hypertension. Terapevticheskiy arkhiv. 2004;9:29–34. In Russian.

19. Nanchikeeva ML, Kozlovskaya LV, Bulanov MN, Konechnaya EY, Gladkaya A. Significance of ultrasonic diagnostics in research of cardiorenal relationship in arterial hypertension. Ultrasonic and functional diagnostics. 2005;1:76–82. In Russian.

20. Nanchikeeva ML. Early stage of renal damage in patients with arterial hypertension: clinical significance, principles of prevention. Abstract of P. H.D. thesis. Moscow. 2010:1–46. In Russian.

21. Bobkova IN, Chebotareva NV, Kozlovskaya LV, Varshavskiy VA, Golitsina EP. Urinary excretion of MCP-1 and TGF-β1 as a marker of chronic glomerulonephritis progression. Terapevticheskiy arkhiv. 2006;78(5):9–14. In Russian.

22. Bobkova IN. Cellular and molecular mechanisms of nephrotoxic action of proteinuria: role in chronic glomerulonephritis progression, way of influence. Abstract of P. H.D. thesis. Moscow. 2007:1–48. In Russian.

23. Schrijvers BF, Flyvbjerg A, De Vriese AS. The role of vascular endothelial growth factor (VEGF) in renal pathophysiology. Kidney Int. 2004;65(6):2003–2017.

24. Fogo AB, Kon V. The glomerulus — a view from the inside the endothelial cell. Int J Biochem Cell Biol. 2010;42(9):1388–1397.

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