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MODERN DIAGNOSTIC MARKERS OF NEPHROPATHY IN PATIENTS WITH ARTERIAL HYPERTENSION AND DIABETES MELLITUS

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Annotation
Currently, proteinuria, serum creatinine and glomerular filtration rate are considered markers of kidney damage. In chronic kidney disease, these markers reveal an already late stage of kidney damage, when drug therapy is not always effective and the process of kidney damage is not reversible. Therefore, in recent years, much attention has been paid to the search for the so-called biomarkers of acute and chronic renal damage, which allow early detection of pathological changes in the kidneys and determine their nature, differentiate damage to different parts of the nephron, accurately determine the stage of the process, assess the severity of inflammation and the intensity of fibrogenesis. Among the new markers that are increasingly being explored, type IV collagen, cystatin C, and aldosterone are of the greatest importance. This review briefly reviews the latest major studies in this area.

Keywords: biomarkers of kidney damage, type IV collagen, cystatin C, aldosterone.

СОВРЕМЕННЫЕ ДИАГНОСТИЧЕСКИЕ МАРКЕРЫ НЕФРОПАТИИ У БОЛЬНЫХ АРТЕРИАЛЬНОЙ ГИПЕРТОНИЕЙ И САХАРНЫМ ДИАБЕТОМ

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Аннотация
В настоящее время маркерами повреждения почек принято считать протеинурию, креатинин сыворотки крови и скорость клубочковой фильтрации. При хронической болезни почек данные маркеры выявляют уже позднюю стадию поражения почек, когда лекарственная терапия не всегда эффективна и процесс поражения почек не обратим. Поэтому в последние годы большое внимание уделяется поиску так называемых биомаркеров острого и хронического почечного повреждения, позволяющих проводить раннее выявление патологических изменений в почках и определять их характер,

дифференцировать поражение разных отделов нефрона, точно установить стадию процесса, оценить выраженность воспаления и интенсивность фиброгенеза. Среди новых маркеров, которые все более активно исследуют, наибольшее значение имеют Коллаген IV типа, цистатин С, алдостерон. В данном обзоре коротко рассмотрены данные последних крупных исследований в этой области.

Ключевые слова: биомаркеры повреждения почек, Коллаген IV типа, цистатин С, алдостерон.

ARTERIAL GIPERTENZIYA VA QANDLI DIABETI BOR BEMORLARDA NEFROPATIYANINING ZAMONAVIY DIAGNOSTIK MARKERLARI.

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Annotatsiya
Hozirgi vaqtda proteinuriya, qon zardobidagi kreatinin va glomerulyar filtratsiya darajasi buyrak shikastlanishining belgilari hisoblanadi. Surunkali buyrak kasalligida bu belgilar buyrak shikastlanishining allaqachon kech bosqichini ko'rsatadi, bunda dori terapiyasi har doim ham samarali bo'lmaydi va buyrak shikastlanishi jarayoni qaytarilmaydi. Shu sababli keyingi yillarda buyraklardagi patologik o‘zgarishlarni erta aniqlash va ularning xarakterini aniqlash, nefronning turli qismlarining shikastlanishini farqlash imkonini beruvchi o‘tkir va surunkali buyrak shikastlanishining biomarkerlarini izlashga, jarayonning bosqichini aniqlash, yallig'lanishning og'irligini va fibrogenezning intensivligini baholashga katta e’tibor qaratilmoqda.. Ko'proq o'rganilayotgan yangi markerlar orasida IV turdagi kollagen, sistatin C va aldosteron eng katta ahamiyatga ega. Ushbu maqola shu sohadagi so'nggi yirik tadqiqotlarni qisqacha ko'rib chiqadi.

Kalit so'zlar: buyrak shikastlanishining biomarkerlari, IV tip kollagen, sistatin C, aldosteron.

Type IV collagen forms the main structure of the basement membrane and mesangial matrix of the glomeruli of the kidneys, is a high molecular weight fibrillar protein with a molecular weight of approximately 540 kDa, consists of α3, α4 and α5 chains and, as a rule, is not filtered through the glomerular basement membrane. Persistent hyperglycemia in DM activates metabolic, profibrogenic, rheological processes in the

renal parenchyma, resulting in excessive synthesis and accumulation of type IV collagen in the glomeruli, followed by the development of glomerular sclerosis. With the accumulation of type IV collagen and its metabolites, their excretion in the urine increases, which is proposed to be used as a prognostic marker for diabetic nephropathy in diabetes mellitus [36].

Determination of the urinary excretion of type IV collagen has been proposed as a test to assess fibrogenesis in the kidneys [30,16]. Type IV collagen is the main component of the basement membranes of the glomeruli and tubules, as well as the mesangial matrix of the renal glomeruli. Accumulation of type IV collagen in the basement membranes and mesangium is one of the earliest morphological signs of diabetic nephropathy, which occurs in some patients before an increase in urinary albumin excretion [29].

Urinary excretion of type IV collagen is a highly sensitive marker for early non-invasive diagnosis of diabetic and hypertensive kidney disease in the initial stages [32].

The levels of albuminuria and type IV collagen in the urine reflect the degree of decrease in kidney function in patients with arterial hypertension [8, 35, 5, 9].

An increase in the excretion of type IV collagen in hypertensive patients indicates the initiation of nephrosclerosis processes, and the presence of obesity exacerbates this process. [38].

Early diagnosis, prevention of formation and targeted regression of glomerulo- and/or tubulointerstitial fibrosis in patients with progressive chronic nephropathies, regardless of their etiology, are the leading direction of modern fundamental and clinical nephrology [37,34,11]. The progression of kidney disease is the result of an imbalance between pro- and anti-inflammatory, proliferative and fibrosing factors [4].

One of the actively studied growth tyrosine kinases is collagen receptors - Discoidin domain receptors (DDR1). In humans, the DDR1 gene is localized on the short arm of the 6th chromosome at the 6p21.3 locus [1]. Evolutionarily, DDR genes encoding DDR are responsible for cell adhesion, proliferation, and remodeling of the extracellular matrix. DDR1 acting as collagen receptors are predominantly found in the epithelial cells of the breast, brain, lungs, kidneys, and gastrointestinal tract [13, 24]. Five isoforms of DDR1 (DDR1a–e) are known. Of these, DDR1b and DDR1a are present in the kidneys. They are activated by collagen types I–VI and VIII [2].

Receptors with tyrosinase activity DDR1, activated by collagen, are simultaneously mediators in proliferation, fibrosis, and inflammation. Their study is a promising direction aimed at preclinical diagnosis of structural changes in tubulointerstitium

associated with a latent inflammatory process and, as a result, its sclerosis. The study of DDR1 in the blood serum of patients with chronic pyelonephritis (CP) revealed their statistically significant excess of the conventional norm in patients with secondary CP occurring against the background of obstructive uropathy, despite the previously diagnosed state of clinical and laboratory remission. This gives grounds to attribute this category of patients to a high risk group for the development of complications of chronic pyelonephritis associated with structural restructuring of the tubulointerstitium and a decrease in renal functions, and in patients with chronic pancreatitis with a history of renal metabolic disorder, the formation of reflux nephropathy [33].

Aldosterone plays a major role in maintaining the sodium-potassium balance in the body: it retains sodium ions and promotes the excretion of potassium ions, thereby maintaining extracellular homeostasis and blood pressure.

In 1960, the sequence of biosynthesis of aldosterone from cholesterol in the adrenal glands was established: cholesterol -> pregnenolone -> progesterone -> 11-deoxycorticosterone -> corticosterone -> 18-hydroxycorticosterone -+ aldosterone. In animals, all 3 zones of the adrenal cortex contain a set of enzymes that provide steroidogenesis, however, in humans, only the glomerular zone contains an enzyme that ensures the formation of 18-hydroxycorticosterone. Thus, in humans, aldosterone synthesis occurs exclusively in the zona glomeruli.

The clinical significance of aldosterone, as already noted above, was partially determined by the work of Conn, who described a syndrome with hypertension and hypokalemia in a patient with an isolated autonomous tumor of the adrenal cortex. This initiated the formation of the concept of a deep relationship between renin and aldosterone and the existence of 2 forms of hyperaldosteronism: with suppressed renin activity (primary hyperaldosteronism) and with increased renin activity (secondary hyperaldosteronism). Thus, it has been recognized that certain forms of hypertension are accompanied by sodium retention, increased potassium excretion, and edema due to increased secretion of aldosterone.

Aldosterone is directly or indirectly involved in the development of essential hypertension, both by increasing its secretion and by changing the sensitivity of its receptors in target tissues. [31]

Effects of aldosterone on salt transport and blood pressure regulation

Aldosterone is well known to increase sodium reabsorption and potassium secretion by the kidney. It exerts its main effects on sodium and potassium balance by binding to the mineralocorticoid receptor (MCR) located in the distal convoluted tubule,

connecting segment and cortical collecting duct in the kidney. The net effect is that aldosterone functions homeostatically to maintain normal sodium and potassium balance as well as blood pressure and circulating blood volume [23]. In addition mineralocorticoid receptors are also present in glomerular endothelial cells, mesangial cells and podocytes as well as the renal and systemic vascular endothelial tissues [6,27]. In the systemic vasculature, heart and kidney aldosterone has mitogenic effects on a number of cell types and therefore has the potential for a pathological role in cardiovascular and kidney disease [10].

Pathologic role of aldosterone in kidney and cardiovascular disease

Aldosterone has been shown to play a major pathologic role in causing cardiovascular and renal injury through multiple mechanisms including inflammation, oxidative stress, activation and enhancement of angiotensin II and accelerated fibrosis [17, 3, 12, 7]. After binding to the mineralocorticoid receptor, aldosterone is translated into the nucleus, where the complex dissociates and binds to regulatory regions of multiple genes that stimulate production of proteins involved in both sodium and potassium transport as well as inflammation and oxidative stress. Activation of serum- and glucocorticoid-inducible kinase 1 (Sgk1) and epithelial sodium channel subunit and glucocorticoid induced leucine zipper is followed by downstream actions that promote both ion transport and inflammation. Hence activation of NADPH oxidase in turn activates NF-b and AP-1 leading to upregulation of intercellular adhesion molecule -1 (ICAM-1), monocyte chemotactic protein-1 (MCP-1), interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1) and transforming growth factor -beta (TGF-b). In the kidney the upregulation of these molecules contributes to vascular injury, tubulointerstitial inflammation and subsequent fibrosis, and glomerular injury during aldosterone infusion accompanied by high salt intake in animal models. In addition, aldosterone inhibits nitric oxide synthase thereby reducing nitric oxide availability in the kidney and vasculature [28].

In recent decades, podocytes and their involvement in the pathogenesis of various proteinuric forms of kidney damage, not only hereditary, but also acquired, including DN, have been the subject of close attention and scientific research in nephrology.

The prerequisites for this line of research were experimental studies that demonstrated the important role of podocytes in maintaining the normal structure and function of the renal glomerulus and the key role of these disorders in the development of PU and the progression of glomerulosclerosis [3,17,19,12].

Hyperglycemia affects podocytes, glycosylation end products (AGEs), components of the activated renin-angiotensin-aldosterone system (RAAS), intraglomerular

hypertension, oxidative stress and other factors and leads to damage to the complex of adhesive proteins that anchor podocytes to the glomerular basement membrane (GMB), to the rearrangement of the actin cytoskeleton with the development of the effect of smoothing podocyte processes, enhanced apoptosis of podocytes, followed by their exfoliation from the BMC and urinary excretion of both whole cells (podocyturia) and individual podocyte proteins (nephrin, podocin, etc.) [18,21,22 ,25]. It is important that ultrastructural and functional disorders in podocytes precede the increase in albuminuria and can be detected even with a short course of DM, which determines another important aspect of the study of markers of podocyte dysfunction - for early diagnosis and monitoring of the course of DN.

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