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Assessment of relationship of markers of the protective system of the oral cavity and the tubulointerstitial system of the kidney

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Abstract---The features of markers of the protective system of saliva, blood and urine in patients with tubulointerstitial kidney damage were studied in a comparative aspect. For this study, 58 patients were selected with chronic kidney disease, namely tubulointerstitial kidney disease. In the blood, oral fluid and urine, the content of lysozyme, the level of lactoferrin, cystatin and lipocalin-2 were determined by the enzyme immunoassay. It was found that somatic pathology affects both the frequency of occurrence of pathology of hard dental tissues and the clinical picture of the course of major dental diseases. It is noted that a sensitive marker of tubulointerstitial kidney damage is a study in saliva, blood and urine of the activity of lysozyme, lipocalin, cystatin and lactoferrin, which will make it possible to propose therapeutic and prophylactic measures for patients with tubulointerstitial kidney damage. [1,2]

Keywords---tubulointerstitial kidney damage, saliva, oral cavity, lysozyme, dental hard tissues, oral fluid.

Introduction

Attention to the problem of tubulointerstitial kidney damage has naturally increased in recent years, dictated by its high proportion in the pathology of the

urinary system (US), diagnostic difficulties and unresolved issues of therapy. The relevance of the chosen topic is determined by the fact that today somatic pathology occurs in 30% of dental patients [19]. Studies of the state of the oral cavity in patients with chronic kidney disease revealed a high prevalence of diseases of the tissues of the oral cavity and, as a result, a significant need for dental care in this group of patients. In the literature available to us, there are few works that determine the characteristics of the state of the oral cavity, as well as oral fluid, blood and urine in patients with tubulointerstitial kidney damage. Also, in domestic practice, there is no program for providing dental care to patients with tubulointerstitial kidney disease (TKD). [17,18]

The pathogenesis and mechanism of development of TIPP is different: the impact on the renal tissue of the virus circulating in the blood and/or excreted in the urine or its toxins with the appearance of pathognomonic changes in the kidney parenchyma, the development of an immune lesion with the deposition of immune deposits in the epithelium of the tubules or interstitium (in infectious TKD), containing the pathogen antigen, a combination of these processes.

An unfavorable mechanism of action of viruses or molecules encoded by the latter may be the activation of lymphocytes and monocytes with the release of cytokines, which increase the formation of leukotrienes, thromboxane, which contribute to the development of ischemia. [15]

The participation of viruses in the development of immunopathological reactions and the formation of immune deposits deposited on basement membranes has been proven. The direct and indirect cytotoxic effects of the infectious factor on various parts of the nephron with the development of intrarenal hemodynamic disorders are discussed. With the progressive course of tubulointerstitial kidney damage, 99.2% of patients showed inhibition of anti-infective protection, which is characterized by a decrease in the level of secretory immunoglobulins A, the completion of phagocytosis by neutrophils, dysimmunoglobulinemia, combined with infection of the urinary system with viral-bacterial or bacterial pathogens capable of persistence. With the progression of the tubulointerstitial process, it is observed in patients with the persistence of a viral-bacterial infection, reduced anti-infective protection and an increase in free radical oxidation processes.

The basis for the diagnosis of TKD is the generalization of the data of the general clinical examination of the patient and the results of modern paraclinical studies, which allow, on the basis of a clinical and morphofunctional approach, to verify the diagnosis, to identify the primary pathology of other organs and systems (rheumatoid arthritis, diabetes mellitus, systemic lupus erythematosus, hemorrhagic vasculitis, purine metabolism disorder, urolithiasis, essential cryoglobulinemia, Wegener's granulomatosis, Goodpasture's syndrome, solid tumors, lymphomas, monoclonal gammopathy, drug nephropathy, hypertension, chronic hepatitis, etc.) and exclude uropathy (anomalies of the urinary system and blood vessels. Currently, it is a generally recognized possibility diagnosis of TKD on the basis of modern clinical and paraclinical data and functional studies confirming the predominance of damage to the tubules and interstitium. logical approach) and pathogenetic features of the disease in a particular child serves as the basis for rational treatment tactics. Non-immune mechanisms play an

important role in the pathogenesis of TIPP, incl. hormonal-messenger systems: angiotensin II and thromboxane A₂ can cause vasospasm with the development of ischemia of the renal cortex, which leads to dysfunction of the renal tubules (RC). Tubal tubular proteinuria (the inability of the proximal tubules to reabsorb plasma low molecular weight proteins filtered in normal glomeruli) is characterized by: low levels of excreted protein - albumin, lysozyme, - microglobulin and immunoglobulin. [8,10]

It has been proven that lysocymuria depends on the phase of the inflammatory tubulointerstitial process and the functional state of the kidneys, the level of lysozyme in the urine increases with tubular renal failure). Urinary excretion of albumin (microalbuminuria) appears earlier than other signs of renal disorders, which are detected by currently available methods. It has been proven that intensive reabsorption of large amounts of filtered proteins by the epithelium of the proximal tubules leads to the activation of epithelial cells with the expression of genes for inflammatory and vasoactive substances, incl. transforming growth factor (TGF- β), monolithic chemoattractive protein and endothelins. [9] The molecules of these substances, produced in excess amounts by the renal tubules, are secreted through the basal cells into the interstitium, leading to inflammation that precedes nephrosclerosis. The main natural supplier of enzymes in the urine are the cells of the proximal tubules of the nephron, which make up about 42% of the mass of the renal tissue. More than 30 enzymes originating from lysosomes and membranes of the marginal brush border are localized in the epithelium of the proximal tubules. According to the classification of U. Burchardt, the main diagnostically significant enzymes of the nephron tubular epithelium can be divided into three groups depending on intracellular localization: marginal alkaline border enzymes, lysosomal enzymes and cytosol enzymes. [11]

Material and research methods

For this study, patients with chronic kidney disease were selected, namely tubulointerstitial kidney damage - 58 people who were in the nephrology department of the TSDI clinic in Tashkent for the period in 2018-2019. For comparison of laboratory parameters, a control group was taken, consisting of 18 people with a healthy oral cavity and no kidney pathology. At the initial stage, each patient was informed about the nature of the study. With the consent of the patient, the criteria for inclusion in a particular group were determined. Criteria for exclusion from the group: patients aged 35-55 years with diseases of other organs and systems in the stage of decompensation. For a comprehensive clinical assessment of the dental status of patients, the following methods were used: interviewing a patient, examining the oral cavity with an assessment of the condition of periodontal tissues, using indices - a comprehensive periodontal index (CPI), a simplified hygienic index of oral hygiene (OHI-S) according to Green-Vermillion. X-ray diagnostics was performed by orthopantomography.

In the examined patients on an empty stomach, before and after rinsing the mouth, before and after brushing the teeth with toothpastes, mixed saliva was collected for 10 minutes without stimulation, by spitting into a test tube according to the method of V.K. Leontiev and Yu.A. Petrovich. Saliva samples were taken in the morning (08.00). Patients refrained from smoking, drinking,

eating, and brushing their teeth 1 hour before sample collection. Prior to the start of the study, the test tubes with samples were stored in the cold at $t=-30^{\circ}\text{C}$. The mixed saliva was centrifuged at 3000 rpm for 15 minutes, and activity was determined in the supernatant. In the blood, oral fluid and urine, the content of lysozyme, the level of lactoferrin, cystatin and lipocalin-2 were determined by enzyme immunoassay.

The studies were carried out in accordance with the recommendations of the manufacturer of test systems "HUMAN". Immunoenzymatic and biochemical studies were carried out using automatic analyzers of the company. "Mindray". All digital data obtained during the survey were subjected to statistical processing by methods of variation statistics using the Statistica 7.0 software package. Differences were considered statistically significant at $p<0.05$.

Research results and discussion

In the course of a clinical study, the features of the clinical course and the incidence of dental diseases in patients suffering from chronic kidney disease were identified. The method of visual control was used to assess the condition of hard and soft tissues of the oral cavity, dentition. To assess the state of oral tissues, the following indices were used: hygiene according to Green - Vermillion (1964) (IGR-U), papillary-marginal-alveolar (PMA) modified by Parma (1960), bleeding (SBI) according to Mühlermann H.R. (1971) and KPU - the sum of carious, filled and extracted teeth. The degree of tooth mobility and the depth of periodontal pockets were assessed.

For an objective assessment of the subjective sensations of patients, a survey was conducted according to the questionnaires developed by us. The periodontal status of people suffering from chronic kidney disease differed from that of those in the control group. So, in patients suffering from chronic kidney disease, the following indicators of periodontal status were noted. Their incidence of gingivitis and periodontitis was 36.8% and 81.5%, respectively.

The indicator of the intensity of the course of periodontal diseases (KPI index) was equal to 2.46 ± 0.17 arb. units 95.1% of patients needed to remove tartar deposits, and diseases of the oral mucosa were diagnosed in 9.1% of cases. The value of Svrakoff's iodine number in persons suffering from CKD was 2.34 ± 0.14 arb. units, hygiene index - 1.91 ± 0.17 arb. units The frequency of occurrence of dystrophic lesions of periodontal tissues (periodontal disease) was 4.6%. Thus, a clinical study of patients suffering from chronic kidney disease for more than three years made it possible to establish the features of the periodontal status, as well as the course of periodontal pathology. Such patients often suffered from inflammatory and degenerative diseases of periodontal tissues, as well as diseases of the oral mucosa, lips, where complications were more pronounced relative to the comparison group. The incidence of caries and non-carious lesions of the teeth in persons suffering from CKD was 81.7% and 90.5%, respectively.

At the same time, people with CKD more often suffered from non-carious lesions of hard tissues of the teeth (wedge-shaped defects, increased tooth wear, hyperesthesia of the teeth), respectively, in 31.4% and 34.5% of cases. It was also

found that for each examined person suffering from CKD, there were, respectively, 0.67 ± 0.05 and 0.59 ± 0.04 teeth with chronic periapical foci of odontogenic infection. So, in CKD, the CP index was 12.8 ± 1.11 (K- 3.7 ± 1.83 ; P - 5.3 ± 0.47 ; V - 3.2 ± 1.43), and in CP - 13.1 ± 0.91 (K - 3.1 ± 0.24 ; P - 6.8 ± 0.53 ; V - 2.7 ± 0.15). Patients suffering from CKD required treatment and prosthetics in 71.3% and 54.6% of cases, respectively, and 74.5% and 57.8% of cases, respectively. The USP index for patients with CP and CG was 51.2% and 57.6%, respectively.

In general, the study of the dental status of patients suffering from chronic kidney disease showed that somatic pathology affects both the incidence of pathology of hard dental tissues and the clinical picture of the course of major dental diseases. This version coincides with the studies conducted. [5] Therefore, difficulties arise in the treatment of diseases of the teeth, periodontal and oral mucosa in patients suffering from CKD. So, when carrying out dental treatment and preventive measures in patients suffering from chronic kidney disease, it is important not only to ensure the effectiveness of the therapy due to the presence of somatic pathology, but also to prevent complications caused by chronic foci of odontogenic infection. A sensitive indicator of tubulointerstitial kidney damage is, in our opinion, the determination of the activity of lysozyme, lipocalin, cystatin and lactoferrin in saliva, blood and urine, which was the main objective of our research.

Lysozyme (muramidase) is a low molecular weight enzyme. As is known, lysozyme not only cleaves the glycosidic bonds of polyamino sugars of bacterial peptidoglycans, but also participates in the regulation of the permeability of tissue barriers, regeneration and healing of oral wounds. Lysozyme enters the saliva as a result of active secretion by mononuclear phagocytes, as well as the destruction of polymorphonuclear leukocytes, which contain it in large quantities. As can be seen from the presented research results (Table 1), the content of lysozyme in saliva in patients with TKD exceeded the initial level by 1.6 times, which indicates an increase in the local protective system of the oral cavity in the examined individuals.

The kidneys are the organ with the highest content of it. As you know, serum lysozyme is formed from decaying granulocytes and monocytes. As these cells are destroyed, it passes into the plasma, where it is in a free state, easily filtered in the glomeruli, and reabsorbed in the proximal tubules. As for the origin of urine lysozyme, there is a theory about its synthesis in the epithelial cells of the renal tubules.

When determining lysocymuria in patients with TCD, compared with healthy individuals, a significant increase in its level by an average of 8 times was found. As is known, up to 500 mg of lysozyme is produced per day, and the period of stay in plasma is short - 75% of the protein is removed within 1 hour, mainly by the kidneys. A decrease in the level of lysozyme in the blood and an increase in its concentration in the urine, i.e. its increased urinary excretion, observed in our studies, indicates a violation of the functional activity of the proximal tubules in this group of patients. The observed change in the level of lysozyme in saliva, according to some researchers, is due to an increase in mucus formation, which leads to a decrease in the antibacterial, antiviral activity of the mucous membrane

and activation of inflammatory processes in the mucous membrane lining of the oral cavity and periodontium [6,9].

Lactoferrin is synthesized in neutrophils and macrophages, blocks complement reactions, enhances the functional activity of neutrophils, their bacteriostatic and bactericidal action. In a number of pathological conditions, lactoferrin is involved in the formation of endothelial injury syndrome and platelet aggregation.

Table 1

The content of biochemical parameters of mixed saliva and urine in patients with CGP combined with CKD

Indicators	Object of study	unit of measurement	Healthy n=18	Sick n=58
Lysozyme	blood	mg/l	12,81±0,82	2,43±0,17*
	saliva	gr/l	0,022±0,001	0,013±0,001*
	urine	mg/l	2,47± 0,19	19,76±1,43*
lactoferrin	blood	mg/ml	1,03±0,09	1,53±0,12*
	saliva	gr/l	4,83±0,26	5,68±0,37*
	urine	mg/ml	28,54±1,47	186,71±9,51*
Cystatin C	blood	mg/l	0,68±0,05	1,75±0,18*
	saliva	mg/ml	2,32±0,17	3,97±0,28*
	urine	mg/ml	1,72±0,01	24,93±1,84*
Lipocalin-2	blood	mg/l	1 ,58±0,11	8,43±0,61*
	urine	mg/ml	5,47±0,43	39,68±2,43*

Note: * - reliability of differences $P < 0.05$ when comparing the indicators of a group of healthy individuals.

It has been established that the diagnostic and prognostic value of tests for lactoferrin increases if the levels of lactoferrin are compared with its serum levels. Based on this, we decided to study the level of lactoferrin in blood, saliva and urine in patients with TKD. As can be seen from the presented research results, the level in the three liquids has a single dynamics, i.e. increased relative to the comparison group. The highest values of reactive protein were noted in the urine of the examined persons, on average 6.5 times compared with the indicators of healthy individuals. A high level of lactoferrin in the urine maintains a change in the phases of the cell cycle in the focus of acute inflammation and slows down the change of polymorphonuclear leukocytes to a population of macrophage monocytes. It is possible that high levels of lactoferrin in saliva are involved in the regulation of osteoblast activity. Thus, despite the fact that studies of lactoferrin

have been conducted since the second half of the last century, the study of its new properties and diagnostic capabilities continues all over the world, due to which studies of lactoferrin in various body fluids remain relevant today.

Cystatin C is a low molecular weight endogenous inhibitor of cysteine proteinases. Cystatin C as an indicator of kidney dysfunction, unlike creatinine, is an almost ideal indicator, since its concentration in the blood is not related to the nature of nutrition, body weight, sex, age. An increase in these biomarkers was found in patients with kidney damage, compared with patients without kidney damage. Therefore, the determination of the level of cystatin C in the urine seems to be promising, since when calculating the GFR, it makes it possible to assess the functional state of the kidneys. The analysis of the results of the studies showed a significant increase in the level of cystatin C in the urine by an average of 15 times in patients with TIPP. An increase in periodontal dystrophic processes in this contingent of patients against the background of TIPP was accompanied by an increase in the level of cystatin C in the blood by 2.6 times and in saliva by 1.7 times. In our opinion, the identified changes in the tissues of the oral cavity and the establishment of a pathogenetic relationship between manifestations in the oral cavity and with chronic kidney disease allow us to formulate certain approaches in the prevention and treatment of oral tissues in patients with TKD.

Lipocalins are proteins secreted into the blood and other body fluids that are able to bind siderophores, small hydrophobic iron-transporting proteins. An important role of lipocalin in the processes of apoptosis and adaptation of degrading tissues is evidenced by the facts of increased synthesis of this lipocalin in damaged tissues. It is involved in the stimulation of the proliferation process in damaged cells, primarily epithelial cells, and protection against bacterial infection, since this protein has a bacteriostatic effect. Haase-Fielitz A. et al. in 2009 found a sharp increase in the concentration of this protein in the cells of the proximal tubules during reperfusion of an ischemic kidney. An increase in blood lipocalin by 5 times is apparently due to endogenous intoxication and the release of reactive protein into the blood in patients with TKD. An increase in the synthesis of lipocalin in the cells of the proximal tubules and its release into the urine by an average of 7 times is caused by disorders associated with ischemia of the renal parenchyma and its lesions with nephrotoxic compounds in the examined individuals.

Thus, the study of dental diseases in patients with TKD and the obtained results of markers of the proximal tubules of the kidneys in this group of patients allow us to propose therapeutic and preventive measures for patients with TIPP aimed at improving the quality of their treatment and life.

Conclusions

1. The study of the dental status of patients suffering from chronic kidney disease showed that somatic pathology affects both the incidence of pathology of hard dental tissues and the clinical picture of the course of major dental diseases.
2. It was revealed that a sensitive marker of tubulointerstitial kidney damage is the study of the activity of lysozyme, lipocalin, cystatin and lactoferrin in

saliva, blood and urine, which allows us to propose therapeutic and preventive measures for patients with TKD.

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