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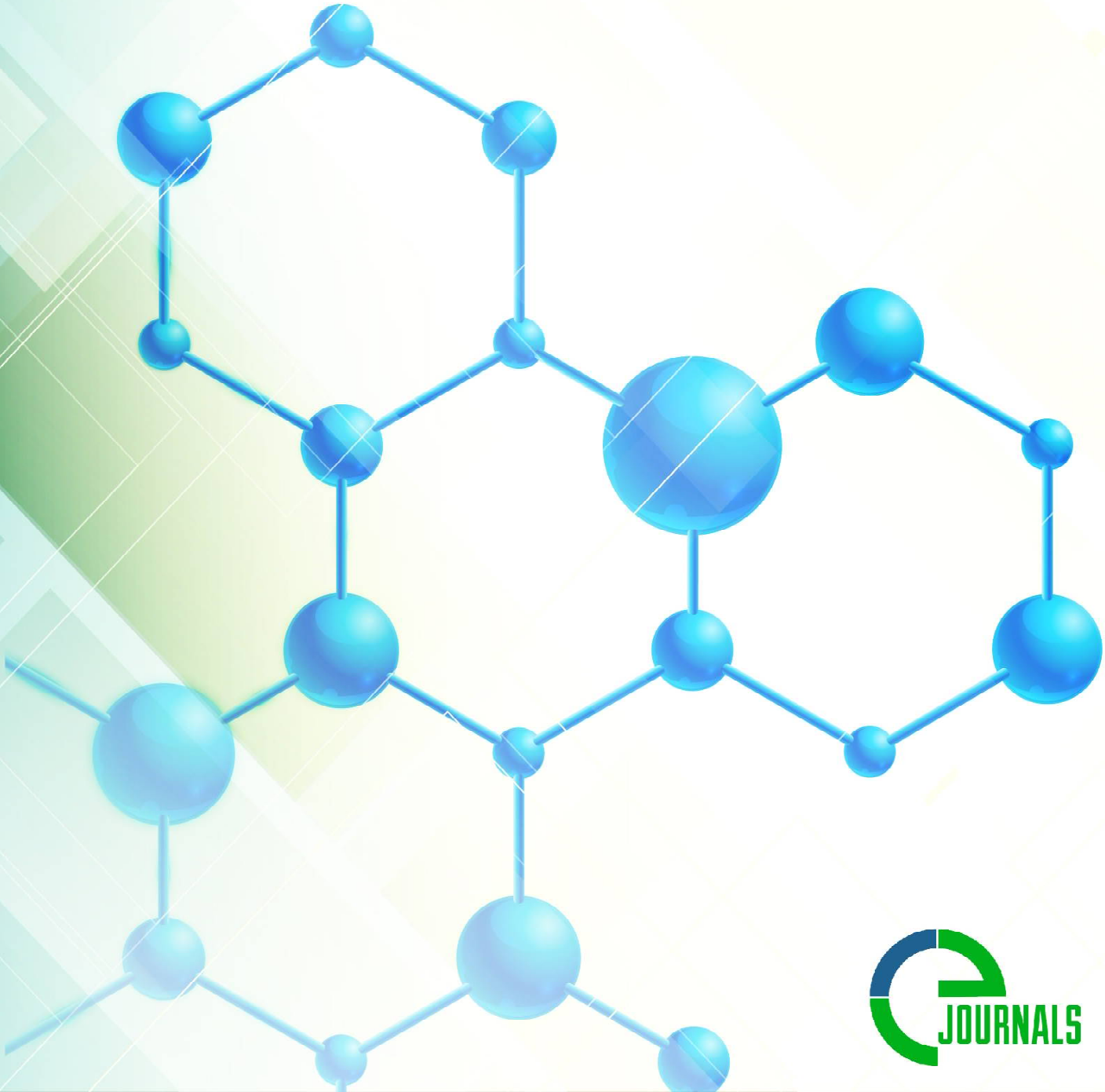

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THE SIGNIFICANCE OF POLYMORPHIC GENES OF MATRIX METALLOPROTEINASES (MMP) AND THEIR TISSUE INHIBITORS IN THE DEVELOPMENT OF DISORDER OF KIDNEY FUNCTION IN CHRONIC GLOMERULONEPHRITIS IN CHILDREN

N.S. Bazarova
bozorovanigina72@gmail.com
Sh.Kh. Ziyadullaev
Samarkand State Medical Institute, Republic of Uzbekistan, Samarkand

Abstract. In children, glomerulonephritis is a disease characterized by rapid progression and complication caused by an irreversible process of the renal glomeruli. Currently, methods of molecular diagnostics have begun to actively develop, which not only complement traditional research methods, but also provide insight from the point of view of molecular pathophysiology. It is expected that a key role in the diagnosis of kidney disease is played by the identification of genes and their changes in the course of the disease, which predict the course of the disease. Changes in chromosomal polymorphic genes of matrix metalloproteinase and its tissue inhibitors, as well as how this change manifests itself in chronic glomerulonephritis, were determined in the prognosis of the disease.

Key words: chronic glomerulonephritis, matrix metalloproteinase, tissue inhibitor.

Introduction. Diseases of the urinary system, according to WHO, currently occupy the 2nd place among the main forms of clinical pathology inherent in childhood, and chronic glomerulonephritis has been steadily progressing over the past 10 years and accounts for 36.76% of all kidney diseases. [1,2]. Over the past decade, great efforts have been made to study the etiology and pathogenesis of glomerulonephritis. Foreign and Russian studies have shown that this phenomenon is based on a complex interaction of genetic factors. About 30-50% of patients with chronic glomerulonephritis have elevated levels of inflammatory markers in their blood. [3.4]

In recent works devoted to the study of pathological processes occurring at the gene level in kidney pathology, it was revealed that the pathogenetic mechanisms of chronic glomerulonephritis can be considered the activation of a systemic inflammatory reaction with the formation of an excess of oxidative stress products and imbalance in the "proteolysis-anti proteolysis" system.All this can enhance the processes of tissue remodeling. Matrix metalloproteinases (MMPs) are considered key effectors of tissue remodeling. These are proteins, the expression of which is present in all tissues at different stages of ontogenesis and is activated under conditions of intensive tissue rearrangement.

The involvement of MMPs in the pathogenesis of diseases makes them an attractive target for drugs. [7] The most obvious impetus for the study of MMP and TIMP is the need to treat diseases associated with abnormalities in tissue structure. The results of experimental and clinical studies obtained to date confirm the role of the MMP / TIMP system in the pathogenesis of diseases. Six representatives of MMP-1,2,3,9,13,14 were identified in the kidneys. Tissue inhibitors regulate MMP and are in a 1: 1 ratio. TIMP-2 is a universal inhibitor. MMP-9 genes, like many other genes, are characterized by polymorphism. Polymorphic genetic loci may not cause any changes in the phenotype, but may have a functional effect, affecting the level of gene expression and the amount of protein product.

According to numerous studies, single nucleotide substitutions in gene regions significantly affect the change in the protein structure, leading to a disruption of the

encoded protein, which may contribute to the development of the disease [8]. Numerous molecular genetic studies are devoted to the study of the polymorphism of genes involved in the processes associated with the development of chronic diseases. At the present stage, polymorphism of candidate genes is being actively studied as one of the potential risk factors for the development of a pathological process. Thus, the study of the association of genetic polymorphisms in the pathogenesis of this pathology seems to be the most urgent. Taking into account the proven participation of the matrix metalloproteinase system in the development of chronic hepatitis, we considered it important in our work to study the polymorphic variants of MMP genes and their tissue inhibitors (TIMPs).

Genetic studies of the MMP-9 genes and their tissue inhibitors TIMP-2 were carried out in the immunoregulation laboratory of the Institute of Immunology and Human Genomics of the Academy of Sciences of the Republic of Uzbekistan. In the DNA of blood leukocytes of sick and practically healthy children, gene polymorphism was determined. DNA isolation was performed by a standard nucleosorption method using Diatom ™ DNAPrep 200 kits (IsoGen Laboratory, Moscow, Russia). DNA samples are typed using a specific oligonucleotide primer with gene regions. PCR analysis using GenePak ™ PCRCore DNA PCR Amplification Reagent Kit (IsoGen Laboratory LLC).

We examined 40 children with chronic hepatitis at the age from 5 to 17 years. who were treated in the nephrology department of the ODMMC. All examined children were tested for the level of polymorphic genes MMP-9 and TIMP-2 in the blood by PCR analysis. In the DNA of blood leukocytes of patients, gene polymorphism was determined. The isolated DNAs were analyzed by the standard nucleosorb method using the Diatom ™ DNAPrep 200 kits (IsoGen Laboratory, Moscow, Russia). DNA samples were typed using a specific oligonucleotide primer with gene regions. PCR analysis using a set of reagents for PCR amplification of DNA GenePak ™ PCRCore (LLC “IsoGen Laboratory”). To standardize the results, the ratio of MMP-9, TIMP-2 to the level of Cystatin C in the blood of patients was calculated. All patients with chronic hepatitis showed a decrease in MMP-9, which corresponds to the development of inflammation and accumulation of extracellular matrix proteins, and the amount of TIMP-2 increased, which is a sign of the risk of developing sclerotic changes in the kidney tissue. Accordingly, these changes affect the glomerular filtration rate (GFR). Cystatin C is the gold marker for GFR. Determinations of Cystatin C were carried out in the SWISS-LAB clinical diagnostic laboratory in Tashkent in the “CYSTOMER” apparatus. Blood sampling was carried out in accordance with the rules of the biochemical research stage. Serum was obtained by centrifuging samples at 3000g for 10 min. The concentration level of cystatin C was investigated using commercial kits "KonelabT-Series CYSTATIN-C" (Finland). The determination of cystatin C in the presented kit is based on the principle of immunoturbidimetry. The measured concentrations are in the range of 0.44-7.0 mg / l. The reference intervals offered by the reagent manufacturer are 0.40-1.20 mg / L for the age group 5 to 17 years. In all age categories, the amount of Cystatin C exceeded the norm, and it was directly proportional to the level of TIMP-2. The connection of MMP and TIMP with Cystatin C explains the aggravation of the process.

Monitoring the parameters of polymorphic genes MMP-9 and their tissue inhibitors TIMP in the immune-inflammatory process in the renal tissue is of great importance in a complex of studies in patients with chronic glomerulonephritis. Determination of this marker is necessary when assessing the development of chronic glomerulonephritis in children. The data obtained can be used for early diagnosis of the sclerotic process, assessment of the prognosis and outcome of the disease, monitoring the ongoing therapy in children with chronic glomerulonephritis. Determination of the pathogenetic significance of the MMP-9 and TIMP-2 polymorphic genes in the development of chronic glomerulonephritis in children is the basis for further study of the MMP and TIMP genes.

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