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Clinical and Laboratory Markers of The Development and Progression of Renal Damage in Patients with Systemic Scleroderma

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Abstract

To Studying the clinical and laboratory signs of the development and progression of kidney damage in patients with systemic scleroderma is an urgent scientific and practical task. Investigating the clinical and laboratory markers of scleroderma nephropathy not only allows for a deeper understanding of the mechanisms of kidney damage in systemic scleroderma, but also improves early diagnosis, disease activity monitoring, disease course prediction, and the individualization of therapeutic and preventive measures.

Keywords: Systemic scleroderma, scleroderma nephropathy, laboratory markers, renal damage.

1. Introduction

TS is a complex autoimmune disease characterized by chronic and progressive connective tissue fibrosis. The triggers for the development of systemic scleroderma (SS) have been only partially identified: prolonged Reynaud syndrome (RS), certain chemicals and silicone breast implants, frequent thermal or other mechanical trauma, predominantly in the acral areas of the body, and steroid hormone imbalance, i.e., stress. Both endogenous and/or exogenous triggering environmental factors/risk factors are important stimulants of epigenetic mechanisms in genetically predisposed subjects [7].

It is well known that RS is a common condition in SS (RS occurs in 95% of SS cases), manifested by changes in the color of the extremities upon exposure to cold [8]. Secondary RS occurs in 15% of patients with primary RS and develops after SS [6]. Primary reversible damage to small vessels, influenced by other factors and an enhanced immune response, leads to secondary RS, causing damage to small vessels and capillaries, and subsequently resulting in tissue fibrosis [3].



In the development of scleroderma nephropathy (SN) in SS, all mechanisms are significant, namely: damage to the microcirculatory bed, increased fibrosis, and immune disorders [1, 6].

In particular, the vascular localization of immune complexes, complement components, and fibrin is considered evidence of the immune nature of kidney damage in SS; specifically, some authors have noted that the immune mechanism plays a special role in the pathogenesis of SN. Vasomotor disorders, developing in the form of vascular spasm and narrowing of the renal artery lumen due to a progressive obliterating process resulting from thrombotic microangiopathy, play an important role in the mechanism of renal damage development. These vascular changes are explained by the development of fibroelastosis in the inner layer of the artery (intima) and fibrosis and arteriosclerosis in the outer layer (adventitia); these severe narrowings lead to tissue ischemia [1, 4, 5].

Even in the absence of clinical signs of kidney damage, the use of functional diagnostic methods helps to detect changes in the kidneys. In previous studies, the main signs of kidney damage in SS were considered to be proteinuria, erythrocyturia, leukocyturia, cylindruria, an increase in blood pressure above 140/90 mmHg, increased urea and creatinine, and a decrease in glomerular filtration rate (GFR) [1, 2].

Improving the outcomes of SN requires early identification of risk factors, accurate diagnosis, and the earliest possible initiation of treatment. Therefore, the need to conduct this study arose.

The aim of the study is to determine the significance of the main traditional and systemic scleroderma-specific risk factors, as well as certain factors causing kidney damage, in the development and progression of nephropathy in systemic scleroderma, and to improve diagnosis.

2. Methods

In accordance with the goals and objectives, the study was conducted between 2022 and 2024 in the cardiorheumatology and rheumatology departments of the multidisciplinary clinic of the Tashkent State Medical University. 70 patients with systemic scleroderma receiving inpatient and outpatient treatment and 28 healthy individuals were selected.

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Materials and methods. In accordance with the goals and objectives, the study was conducted between 2022 and 2024 in the cardiorheumatology and rheumatology departments of the multidisciplinary clinic of the Tashkent State Medical University. 70 patients with systemic scleroderma receiving inpatient and outpatient treatment and 28 healthy individuals were selected.

3. Results

All rheumatic test parameters in the main group of patients differed significantly from those in the control group. For example, antistreptolysin-O (ASLO) levels were 2.2 times higher in patients with highly active TS compared to the control group, RO was 2.8 times higher, and CRP was 14 times higher; meaning that as the disease activity level increases, the rheumatic test parameters also increase.

In the studied patients, the daily proteinuria level was 0.39 g/l in highly active SS, 1.5 times lower in moderately active SS, and 0.08 g/l in low-active SS; proteinuria was not observed in the control group. The leukocyte count in the urine sediment was 7.5 per field of view in the highly active type, and 5.8 and 5.3 in the moderately active and low-active types, respectively; in the control group, it did not exceed 2.2. The erythrocyte count in patients with highly active SS was twice as high as in patients with moderately and low-active SS. Casts were also observed 1.5 times more frequently in patients with the highly active type compared to patients with moderately active and low-active SS. In the control group patients, the aforementioned cells were within normal limits. The minimum (1004-1005) and maximum (1014-1016) relative urine density were observed to be almost identical in patients across all 3 activity levels, while the range was the lowest in patients with highly active SS at 9.5, nearly the same in patients with moderately active and low-active SS (10.5 and 12.5, respectively), and 16 in the control group patients.

The patients in the study underwent 24-hour ambulatory blood pressure monitoring (ABPM).

Analysis of the ABPM parameters in the main group of patients revealed pronounced abnormalities in the 24-hour blood pressure profile, characterized by an increase in the mean 24-hour blood pressure values, an insufficient decrease at night, and increased variability.

The mean 24-hour values of systolic blood pressure (SBP) in patients with systemic scleroderma were 138.6 ± 14.2 mmHg, and diastolic blood pressure (DBP) was 86.3 ± 9.7 mmHg,



which were statistically significantly higher than the control group values (118.1 ± 9.2 mmHg and 74.2 ± 6.5 mmHg, respectively) ($p < 0.05$).

Daytime blood pressure values in the main group of patients were also significantly higher than in the control group. Nighttime values of SBP and DBP remained elevated, indicating a disruption in the circadian regulation of blood pressure and an insufficient decrease in blood pressure at night.

In patients with SN, the hypertension time index was significantly increased, reflecting a high-pressure load on target organs, primarily the kidneys.

Doppler ultrasonography of the renal vessels was performed in patients of the main and control groups of the study.

The main hemodynamic parameters in the segmental and interlobular arteries of the kidneys were evaluated: peak systolic blood flow velocity (PSV), end-diastolic velocity (EDV), resistance index (RI), and pulsatility index (PI).

Analysis of the obtained data showed that patients with systemic scleroderma and nephropathy exhibit pronounced impairments of intrarenal hemodynamics, characterized by increased vascular resistance and decreased renal tissue perfusion.

The resistance index in the segmental arteries of the main group patients was 0.76 ± 0.05 , which was significantly higher than the values of the control group (0.64 ± 0.04 , $p < 0.05$). A similar trend was observed in the interlobular arteries.

The pulsatility index was also high, reflecting a decrease in vascular wall elasticity and an increase in peripheral resistance. Additionally, a decrease in the end-diastolic blood flow velocity was noted, indicating impaired renal perfusion.

A statistically significant increase in the resistance and pulsatility indices in the segmental and interlobular arteries of the kidneys was found in patients with TS and SN. These changes indicate an increase in intrarenal vascular resistance.

A decrease in the end-diastolic blood flow velocity indicates a deterioration in renal perfusion and can be considered an early sign of ischemic damage to the renal tissue.

When cystatin C and TGF- β 1 were measured in the blood and urine of patients in the study's main and control groups, all patients in the main group exhibited levels of these indicators that significantly differed from the control group, i.e., from the

normal range, indicating the presence of SN in all patients in the main group.

When analyzing the determination of TGF- β 1 in the serum urine of the study patients and their levels relative to the main SS indicators, it was noted that TGF- β 1 increases with age; i.e., the highest levels were observed in patients aged 60 and older. The highest level was observed in the subacute course of TS, while the chronic course showed a 1.5-fold decrease in TGF- β 1 levels compared to the subacute course. As TS activity increased, an increase in the level of TGF- β 1 was observed; i.e., at low, medium, and high levels of activity, it was 61.8, 77.7, and 82.6 ng/ml in the blood, respectively. As the stages of TS progressed, the amount of TGF- β 1 in the blood and urine increased.

Analysis of the correlations between various parameters and TGF- β 1 in SS revealed a positive direct correlation with TGF- β 1 cystatin C ($r=0.5$), daily proteinuria ($r=0.5$), leukocytes in the urine ($r=0.4$), patient age ($r=0.4$), SBP ($r=0.4$), disease activity ($r=0.4$), ESR ($r=0.3$), erythrocyte and cylinder counts in the urine ($r=0.3$), and a negative reversible correlation with GFR and maximum urine density ($r=-0.3$).

In patients aged 60 years and older, an increase in urinary excretion of TGF- β 1 was identified in patients with generalized SS, stage 3, and subacute SS.

When analyzing the levels of cystatin C in blood and urine relative to the main parameters of SS, it was found that the level of cystatin C increases with age; i.e., the highest level was observed in patients aged 60 and older. In the subacute course of the disease, the level of cystatin C was 1.4 times higher than in the chronic course. It was established that as SS activity levels increase, the amount of cystatin C also increases; that is, at high levels of activity, the amount of cystatin C reaches its maximum level. In the 1st, 2nd, and 3rd stages of SS, the amount of cystatin C in the blood was 1.3, 2.7, and 3.3 mg/l, and in the urine it was 79.4, 104.3, and 158.6 μ g/l, respectively; as the stages of the disease increased, an increase in the amount of cystatin C was observed.

Analysis of the correlations between certain parameters of cystatin C and SS revealed an inverse negative relationship between SBP ($r=0.5$), DBP ($r=0.4$), disease activity ($r=0.5$), RS ($r=0.4$), TGF- β 1 ($r=0.5$), daily proteinuria ($r=0.5$), leukocyte count ($r=0.4$) and urine cylinders ($r=0.4$), cystatin C and GFR ($r=-0.4$), maximum urine density ($r=-0.4$), and scale density ($r=-0.4$).

To evaluate the diagnostic significance of cystatin C and TGF- β 1 in blood and urine as markers of kidney damage in



patients with systemic scleroderma, a ROC analysis was conducted to determine the area under the curve (AUC), sensitivity, and specificity.

The analysis showed that the studied biomarkers have high diagnostic significance, with the highest prognostic significance recorded for blood cystatin C and urinary TGF- β 1 levels.

The conducted ROC analysis demonstrated that all studied parameters have high diagnostic significance (AUC > 0.90), which allows them to be considered reliable markers of SN in SS.

The largest area under the ROC curve was determined for the urinary TGF- β 1 level (AUC = 0.95). This indicates that it has the highest sensitivity and specificity among the studied indicators. This marker reflects the activity of fibrotic processes in renal tissue and can be used in the early diagnosis of SN.

Blood cystatin C also exhibited high diagnostic value (AUC = 0.93), confirming its significance as a sensitive indicator of reduced GFR and early renal dysfunction.

Urinary cystatin C and blood TGF- β 1 levels were also characterized by high AUC values, but lagged slightly behind the aforementioned markers. The identified cut-off values provide an optimal ratio of sensitivity and specificity.

Consequently, the ROC analysis results indicate the high diagnostic and prognostic significance of cystatin C and TGF- β 1 levels in the blood and urine of patients with systemic scleroderma.

Based on the obtained results, a program was developed to predict the development and progression of scleroderma nephropathy. In accordance with this program, the following indicators were taken as a basis: TGF- β 1 and cystatin C in the blood and urine, GFR, disease activity level, proteinuria, and blood pressure. Based on their results, scores ranging from 0 to 2 points were assigned.

The results were summed up and divided into risk categories. A score of 0-2 points is classified as low risk: a low-activity stage of SN with a very low probability of development, requiring examination every 6 months. If a patient scores 3-5 points, moderate fibrosis has developed, and there is a probability of progression within 1-2 years; monitoring every 3 months is mandatory. 6-9 points indicates high risk and active progression: there is a probability of a decrease in GFR within the next 6-12 months, requiring intensive treatment and monitoring. A score of

10 points or higher indicates a very high risk with a high probability of a scleroderma renal crisis; monitoring every 2-4 weeks is necessary, along with potent antifibrotic and nephroprotective therapy. There is a possibility of a decrease in GFR within the next 6-12 months, which requires intensive treatment and monitoring.

4. Conclusion

1. Age over 60 years and a subacute course of the disease significantly contribute to the development of kidney damage in SS. The presence of these factors is associated with the severity of renal pathology, the development of arterial hypertension, and a decrease in renal function.

2. Significant correlations were identified between GFR, cystatin C, and TGF- β 1 levels in patients with varying degrees of renal impairment.

3. Cystatin C and TGF- β 1 demonstrated high sensitivity, outperforming traditional markers (creatinine, proteinuria) in detecting early and preclinical forms of kidney damage.

4. An increase in serum cystatin C levels in SS reflects the severity of renal damage and a decrease in renal filtration capacity. GFR calculated based on cystatin C levels allows for the assessment of renal filtration function even in the early stages of nephropathy.

5. Based on the obtained results, a prognostic model was developed that allows patients with systemic scleroderma to be classified into groups according to the risk of development and progression of kidney damage.

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