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Systemic Scleroderma Complicated by Chronic Kidney Disease

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Abstract The purpose of this study is to study the incidence of chronic kidney disease (CKD) in patients with systemic scleroderma (SSD). 100 patients with a reliable diagnosis of SSD were examined. The patients underwent general clinical examination and laboratory tests aimed at determining the activity of SSDs and the degree of damage to internal organs. The glomerular filtration rate (GFR) was calculated, the presence of concomitant pathology was taken into account. In 88% of patients with SSD, CKD was detected, in 80% — a decrease in GFR, in 81% — hypostenuria and/ or proteinuria. The relationship between SLE and heart disease in patients with SSD, the degree of pulmonary hypertension, the activity index of Valentini disease, the index of resistance of renal vessels, the presence of concomitant kidney pathology, arterial hypertension and/or coronary heart disease has been established.

Keywords Systemic scleroderma, Chronic kidney disease, Glomerular filtration rate

1. Introduction

Systemic scleroderma (SSD) is a chronic, multisystem disease characterized by the development of fibrosis of the skin and internal organs [1,2]. The disease leads to a deterioration in the quality of life [3,4], characterized by an increase in mortality [5] at a high cost of treatment [6]. To date, the pathogenesis of SSD has not been fully studied, but it has been established that vascular proliferation, obliterating microangiopathy and fibrosis play an important role in it [7], which at a late stage of SSD lead to damage to internal organs [8]. Structural restructuring of the microcirculatory bed and generalized progressive vasculopathy are processes leading to the development of cardiovascular pathology, which is the leading cause of deaths in SSD [9]. At the stage of the disease development when the pathology of the cardiovascular system manifests itself clinically, the probability of slowing the progression of vasculopathy and remodeling of the cardiovascular system against the background of therapy is minimal, and therefore it seems relevant to identify potential markers of initial vasculopathy [8].

The presence of markers of chronic kidney disease (CKD) is considered as factors associated with the development of cardiovascular events, including in the early stages of the disease. It has been shown that CKD — a kidney disease of any etiology lasting more than 3 months, which is manifested by a violation of their function and/or structure with a decrease in kidney function [10] — is an independent factor of unfavorable cardiovascular prognosis both in the general population [1] and in the population of persons with cardiovascular pathology [2]. Patients with CKD are classified as persons at very high risk of developing cardiovascular complications [3-5]. In modern clinical practice, markers of the presence of CKD (for example, microalbuminuria) are used as early preclinical indicators of vasculopathy in patients with diabetes mellitus and hypertension [8]. Data on factors, the presence of which is interrelated with the development of CKD in patients with SDS, are presented sparsely in the literature, and therefore the study of this problem seems relevant to us.

The aim of this study is to study the incidence of CKD in patients with SSD with the analysis of factors associated with impaired renal function in the examined population.

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2. Material and Methods

The study included 100 patients with SSD who were on inpatient treatment in the rheumatology department of the Saratov Regional Clinical Hospital in 2009-2011, who met the diagnostic criteria for SSD of the American Rheumatology Association (1980) and/or diagnostic criteria for SSD developed by N.G. Guseva [16]. The following studies were performed: objective examination of the patient; general blood test; general urine analysis; biochemical blood test with determination of total cholesterol, serum creatinine by the Jaffe method on a Hitachi 912 biochemical analyzer (Japan) using DiaSis reagents (Japan); C-reactive protein was determined by a

highly sensitive photometric turbidimetric method using DiaSis reagents (Japan) on a Hitachi automatic blood analyzer (Japan); in part patients were examined for daily proteinuria, a Nechiporenko test was performed. The presence of hypostenuria was found in the case of a decrease in the density of morning urine less than 1018 against the background of dry eating. The glomerular filtration rate (GFR) was calculated using the Cockcroft—Gault formulas [17], MDRD (Modification of Renal Disease Study) [18] and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) [19]. Ultrasound examination of the kidneys and duplex examination of the renal arteries with the calculation of the vascular resistance index (Acuson 128 XP/10), electrocardiography were performed. Echocardiography was performed on the Acuson 128 XP/10 complex, using M—modal mode, two-dimensional (B) mode, pulse and constant-wave Doppler modes in standard echocardiographic positions [20]. Systolic pressure in the pulmonary artery (SDLA) was assessed when registering a trancuspid flow in the mode of constant-wave Dopplerography. The maximum flow rate of tricuspid regurgitation was determined, according to which the systolic transtricuspid pressure gradient was calculated using the modified Bernoulli equation. In the absence of pulmonary artery stenosis, SDLA is equal to the sum of the systolic transtricuspid pressure gradient and systolic blood pressure in the right atrium. The presence of pulmonary hypertension was found at the SDLA level of 36 mmHg or more.

X—ray examination of the hands, feet, and chest organs was performed in all patients, and high-resolution computed tomography was performed in some patients.

A modified G. Rodnan score was used to assess the severity of skin compaction [21]. Diffuse and limited forms of SSD were distinguished [5]. To assess the activity of SSDs, the Valentini activity index (European Scleroderma Study Group, 2001) was calculated [21-25].

The analysis took into account the peculiarities of patient treatment: 56% of patients received D-penicillamine, glucocorticoids — 67%, nonsteroidal anti—inflammatory drugs — 56%, alprostadil — 13%, basic drugs — 20% of patients (of which 6% — methotrexate, 11% - 4—aminoquinoline drugs, 3% - cyclophosphamide). Program therapy with cyclophosphamide and glucocorticosteroids for fibrosing alveolitis was received by 10% of patients.

Statistical processing was carried out using Microsoft Offi ce Excel 2007 (Microsoft Corp., USA) and Statistica 8.0 (StatSoft Inc., USA) programs. The nature of the data distribution was evaluated graphically and using the Shapiro—Wilk criterion. The description of features with a normal distribution is presented in the form of M ± SD, where M is the arithmetic mean; SD is the standard deviation; for features with a distribution other than normal, the results are presented in the form of Me [Q1; Q3], where Me is the median; Q1 and Q3 are the first and third quartiles. Parametric methods were used to process data with a normal distribution type: t-test for independent groupings, paired t-test. When the data distribution was different from normal, nonparametric methods were used: the Mann—Whitney criterion, the Wald—Wolfowitz criterion, the $\chi 2$ criterion, the Wilcoxon criterion, the sign criterion. When comparing more than two independent groupings, methods of variance analysis were used: parametric variance analysis for normally distributed data and Kruskal—Wallis rank analysis of variations for data with a distribution other than normal. To assess the relationship between individual indicators, correlation analysis was used with the calculation of the parametric Pearson coefficient or the nonparametric Spearman correlation coefficient [26].

3. Results and Discussion

88 (88%) patients were found to have CKD (K/DOQI, 2007). The structure of CKD in patients with SSD is presented as follows: stage I was diagnosed in 16 (18.9%) patients, stage II — in 52 (59.1%), stage III — in 21.6%, stage IV — in 1 (1.1%) patient. Chronic renal insufficiency of stage I and II was detected in 3 (3%) of the examined patients.

A decrease in GFR in the range from 60 to 89 ml/min / 1.73 m2 was observed in 60 (60%) patients, from 30 to 59 ml/min/ 1.73 m2 — in 19 (19%); in 1 (1%) patient, GFR was less than 30 ml/min/1.73 m2. Of 19 patients with no indication of kidney disease and cardiovascular pathology, an isolated decrease in GFR of less than 60 ml/min / 1.73 m2 without changes in urinary sediment was found in 22%. Proteinuria was detected in 34 (34%) patients, hypostenuria — in 81 (81%). When analyzing the factors associated with a decrease in renal function, significant differences in the age of patients with varying degrees of GFR reduction were found. This fact is natural, since age is taken into account when calculating the GFR.

When analyzing the associations of GFR with the features of SSD, a significant inverse relationship was revealed between GFR and the activity index of Valentini disease, the level of SDLA, the index of resistance of the renal arteries (according to the duplex study of the renal arteries), the level of hemoglobin and serum cholesterol.

The relationship between GFR and heart disease has been established. In patients with myocardiofibrosis, GFR was 71.17 ± 18.43 ml/min/1.73 m2, without myocardiofibrosis — 80.94 ± 20.11 ml/min/1.73 m2 ($p = 0.02$), in patients with pericarditis — 66.7 ± 17.06 ml/min/1.73 m2, without pericarditis — 78.6 ± 18.92 ml/min/1.73 m2 ($p = 0.004$). In the absence of atrioventricular valve insufficiency, GFR was 89.59 ± 14.12 ml/min/1.73 m2, in case of grade I insufficiency — 80.71 ± 27.56 ml/min/1.73 m2 (differences with the results of patients without valve insufficiency are insignificant, $p = 0.3$), in case of grade II insufficiency — 71.85 ± 17.02 ml/min/ 1.73 m2 (differences with indicators in patients without valve insufficiency are statistically significant, $p = 0.01$), with grade III insufficiency — 69.78 ± 9.06 ml/min / 1.73 m2 (differences with indicators in patients without valve insufficiency are significant, $p = 0.03$).

SDLA in patients with GFR greater than 60 ml/min / 1.73

m2 is 30.63 ± 5.8 mmHg, with a decrease in GFR less than 60 ml/min / 1.73 m2 — 35.79 ± 6.2 mmHg (p = 0.01).

The analysis of concomitant pathology revealed that 77 (77%) of the examined patients have cardiovascular diseases (arterial hypertension, coronary heart disease), 35 (35%) - kidney diseases (chronic pyelonephritis, urolithiasis, congenital anomalies of development and position of the kidneys), 10 (10%) — diabetes mellitus. There were no significant differences in GFR in patients with different clinical forms of SSD (p = 0.14) and skin score values (p = 0.8) in patients receiving different treatment (p > 0.05).

There are several forms of kidney damage in SSD, the most severe of which is sclerodermic renal crisis, which is observed in less than 10% of patients [27]. At the same time, according to autopsies, undiagnosed kidney pathology is detected in 60-80% of patients with SSD [28]. The frequency of detection of CKD obtained by us is consistent with the presented autopsy data. According to clinical studies conducted by P. Canon et al. [29] in 50% of patients who do not have symptoms of the disease, there are clinical markers of renal damage, such as proteinuria and an increase in serum creatinine levels, which is slightly less than the frequency of occurrence of CKD established by us. The data obtained by us indicate that CKD occurs in patients with SDS in 88% of cases (in 78% — in the absence of diabetes mellitus); according to population studies, the frequency of detection of CKD in the general population is 39% [30], i.e. less often than with SDS. In patients with SSD, as in the general population, stage II CKD prevails [30]. This stage of kidney damage does not manifest clinically, but is a factor of unfavorable cardiovascular prognosis. And since patients with SSD are characterized by asymptomatic kidney damage, manifested by proteinuria and characterized by a slow decrease in GFR [30], a targeted search for CKD in this cohort of patients, from our point of view, can and should be carried out without clinical indications for the presence of kidney pathology.

The correlations established by us between the decrease in GFR and the presence of arterial hypertension, diabetes mellitus, and pathology of the urinary system are quite expected, since similar correlations were previously shown in large epidemiological studies involving patients without rheumatic diseases [30]. The revealed correlation between GFR and the disease activity index indicates the fact that the activity of SSDs may be an independent factor in a decrease in kidney function. The data obtained are indirectly confirmed by studies that have shown the presence of a relationship between impaired renal function and the outcome of SSD [8].

The relationship between the presence of sclerodermic heart disease, the degree of relative insufficiency of atrioventricular valves, the degree of pulmonary hypertension and a decrease in GFR is interesting. According to V. Shanmugamand et al. [8], the development of chronic renal failure in patients with SSD is associated with a threefold increase in the risk of secondary pulmonary hypertension, which is a factor independently associated with increased mortality in the population of patients with SSD. In this study, we have shown the relationship between pulmonary hypertension and a decrease in GFR in patients with all stages of renal function decline, including before the development of chronic renal failure. As a possible mechanism of the relationship between a decrease in kidney function and the development of pulmonary hypertension, the formation of endothelial dysfunction against the background of a systemic inflammatory process, the development of chronic renal vasculopathy, the use of nephrotoxic drugs or the development of glomerulonephritis can be considered. The absence of differences in the incidence of CKD in patients receiving different treatments may be due to the small sample size and the lack of data on dynamic follow-up of patients.

The design of this study allows us to state the fact of the presence of a high incidence of CKD in patients with SSD and establish the presence of an association between a decrease in GFR and indicators of disease activity, damage to the cardiovascular system. The fact that 88% of patients with CKD have CKD and, therefore, belong to a group of very high risk of developing cardiovascular complications, it seems important, in connection with which the examination of patients with CKD in order to identify CKD and the calculation of GFR can be recommended for introduction into routine practice of cardiologists, rheumatologists and therapists.

4. Conclusions

The study established the presence of chronic kidney disease in 88% of patients with systemic scleroderma, which makes it possible to classify these patients as persons with a very high risk of developing cardiovascular complications. A decrease in the glomerular filtration rate in the examined patients is associated with the activity of the disease, the presence of myocardiofibrosis, the degree of insufficiency of the atrioventricular valves, the severity of pulmonary hypertension, the presence of concomitant diseases (arterial hypertension, diabetes mellitus, kidney and urinary tract pathology).

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