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Renal problems in scleroderma: pathogenesis, clinical manifestations, and modern treatment methods

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Abstract: Systemic sclerosis (SSc) is an autoimmune disease of connective tissue characterized by fibrosis of the skin and internal organs, vascular damage, and immunological changes. One of the most severe complications is renal involvement, particularly scleroderma renal crisis (SRC). Renal crisis is one of the most serious complications of SSc and often occurs in diffuse SSc. This article discusses the pathogenesis, clinical manifestations, diagnostic methods, and modern approaches to treatment of renal involvement in SSc.

Keywords: Systemic sclerosis, scleroderma renal crisis, chronic kidney disease, renovascular hypertension, antifibrotic therapy.

Introduction: SSc is an autoimmune disease characterized by impaired collagen turnover and progressive fibrosis of connective tissues. The disease affects various internal organs, including the cardiovascular system, lungs, digestive system, and kidneys. Renal involvement in SSc is a serious complication that significantly impacts the patient's quality of life and prognosis. Sclerodermic renal involvement, related to SSc, is a pathological process that develops slowly and manifests as progressive kidney failure [1, 8]. This condition is observed in a significant portion of patients with SSc and is mainly associated with fibrosis of the renal glomeruli, interstitial tissue, and blood vessels. Due to its slow progression, sclerodermic renal involvement often does not manifest clinically in the early stages and can only be detected through laboratory tests. Another form of renal damage in SSc is SRC, which presents with sudden onset of severe hypertension, kidney failure, and microangiopathic hemolytic anemia. SRC is distinguished by its acute and severe progression, while sclerodermic renal involvement is a chronic and slowly progressing process. According to some researchers, scleroderma renal crisis occurs in 5-20% of patients with systemic sclerosis. The disease mainly develops within the first 3-5 years. Among patients with scleroderma renal crisis, 40-50% lose their ability to work due to long-term complications. The mortality rate is 10-20%. In systemic sclerosis, various clinical and morphological forms of nephrological diseases occur, and although their development depends on several factors, all of them affect kidney function. In cases of proteinuria or mild kidney dysfunction, the glomerular filtration rate (GFR) is 60-90 ml/min/1.73m². With the onset of scleroderma renal crisis, the GFR rapidly decreases and may drop below 30 ml/min/1.73m², leading to the development of chronic kidney disease [2]. SSc is a rare but severe systemic disease characterized by endothelial dysfunction, tissue fibrosis, and abnormal immune responses. Renal involvement occurs in 20-50% of patients, and in 10-15% of cases, kidney failure develops, which is a life-threatening condition. This article provides an overview of the pathogenesis, clinical manifestations, and treatment of renal complications in SSc.

Clinical Features

Hypertension: This is a common problem in patients with SSc. Blood pressure remains consistently high,

leading to impaired kidney function. Proteinuria: Kidney damage causes protein loss in the body, which, in turn, leads to nephrotic syndrome. Increased Creatinine and Urea Levels: Due to worsening kidney function, kidney dysfunction can result in the accumulation of toxic substances in the body. Azotemia and Uremia: These conditions are characterized by an increased concentration of nitrogenous compounds in the blood, which occur when kidney filtration function is impaired. If kidney function fails, nitrogenous waste products accumulate, leading to poisoning of the body. Pathogenesis of Renal Involvement in SSc Scleroderma Renal Crisis is the most dangerous and acute manifestation of renal involvement, typically occurring in the diffuse form of systemic sclerosis. This condition is observed in 10-20% of patients and can lead to severe kidney failure [3]. Main Features of SRC: Severe Hypertension (≥180/100 mmHg): This appears as a hypertensive crisis. Headache, Visual Impairment: Damage to the eye blood vessels may occur due to hypertension. Nausea, Vomiting: These symptoms arise from decreased kidney function. Proteinuria (protein in urine): Caused by impaired kidney filtration. Microangiopathic Hemolytic Anemia: Destruction and breakdown of blood cells. Oliguria or Anuria: Reduced urine output or complete cessation of urine production. Rapidly Progressive Kidney Failure: If treatment is delayed, kidney function can completely cease within a few days [4].

Slowly progressive kidney failure. In some patients, kidney damage develops slowly and may remain unnoticed for a long period. Main Clinical Features: Normal or Slightly Elevated Blood Pressure: Unlike acute SRC, blood pressure does not increase sharply. Proteinuria (protein in urine) and Hematuria (blood in urine): Mild or moderate in severity. Decreased Kidney Filtration Function: Creatinine and urea levels gradually increase. Edema (swelling): More prominent in the face, hands, and feet. Oliguria or Anuria: Reduced urine output or complete cessation of urine production. Chronic Kidney Disease (CKD): This can develop over several years [5]. Chronic Renal Failure (CRF): A pathological condition where kidney function gradually deteriorates due to prolonged kidney diseases. This disease decreases the kidneys' ability to filter blood, leading to the accumulation of toxins and excess fluid in the body. Causes of CRF: CRF often develops as a result of other chronic diseases. Main Causes of CRF: Diabetes (Diabetic Nephropathy) Hypertension (High Blood Pressure) Glomerulonephritis (Inflammation of the kidney glomeruli) Polycystic Kidney Disease Autoimmune Diseases (such as scleroderma, lupus) Frequent Recurring Pyelonephritis Medications (NSAIDs, some antibiotics, and toxic substances) [6]. Stages of CRF: CRF develops gradually and may be unnoticed in the early stages. However, as the disease progresses, the following symptoms may appear: Fatigue and weakness itchy and dry skin, loss of appetite, nausea, and vomiting swelling in the arms and legs. Increased blood pressure sensation of tightness and shortness of breath sleep disturbances and difficulty concentrating. Diagnosis of CRF: to diagnose CRF, the following tests and examinations are conducted: Blood tests: Creatinine, urea, electrolytes (Na, K, Ca, P) Calculation of Glomerular Filtration Rate (GFR)Urine tests: Proteinuria, microalbuminuria, erythrocytes. Kidney ultrasound (US) and biopsy (if necessary) [7]. Treatment Methods for CRF: Although CRF cannot be completely cured with specific medications, the progression of the disease can be slowed, and symptoms can be managed. Pressure Control: ACE inhibitors (captopril, enalapril, ramipril) ARB drugs (losartan, valsartan) Diet and Fluid Restrictions: Reduce salt intake (≤ 3-5 g per day). Limit animal protein. Avoid potassium and phosphorus-rich foods. Electrolyte balance monitoring: If hyperkalemia (elevated potassium levels) occurs, potassium intake should be restricted. Use phosphate binders to reduce phosphate levels. Anemia Treatment: Erythropoietin preparations iron and vitamin B12 supplements Dialysis or kidney transplantation: If GFR < 15 ml/min, initiate hemodialysis or peritoneal dialysis kidney transplantation is the most effective method [8].

Main pathogenetic mechanisms of kidney damage in SSc: Endothelial dysfunction: in systemic sclerosis, autoimmune inflammation leads to damage of endothelial cells, resulting in vasoconstriction, platelet activation, microthrombosis, and inflammation. Hypercoagulability and microthrombosis: In SSc, there is an increased tendency to thrombosis, which leads to the development of thrombosis in the kidney capillaries and arterioles. This results in ischemic damage to the kidneys. Microangiopathic Hemolytic Anemia: Damage to the inner layer of blood vessels causes the breakdown of erythrocytes. Fibrosis and interstitial changes: In SSc, excessive activation of fibroblasts and collagen accumulation lead to the hardening of the kidney interstitial tissue. Glomerulosclerosis: damage to the kidney filtration system [3, 9]. Tubulointerstitial Fibrosis: Atrophy of the renal tubules and loss of function. Vascular fibrosis: overactive fibroblasts produce collagen, leading to thickening of the glomerular, interstitial tissue, and vessel walls, which decreases renal blood flow and causes hypertension. Increase in angiotensin II and endothelin: The elevated levels of angiotensin II and endothelin lead to excessive narrowing of the renal blood vessels, which results in decreased GFR and kidney ischemia. Hyperactivation of

the Renin-Angiotensin-Aldosterone System (RAAS): This hyperactivation contributes to an increase in blood pressure and worsens renal blood supply, further impairing kidney function. Immunopathogenesis and Autoimmune Attack: Since SSc is an autoimmune disease, antifospholipid antibodies and other autoantibodies can damage the kidney blood vessels. Inflammatory cytokines (such as TNF-α, IL-6, TGF-β) exacerbate inflammation and fibrosis in the kidney tissues [10]. Activated macrophages and lymphocytes release inflammatory mediators, leading to progressive damage to the glomeruli Arterial Hypertension and Renal Crisis: In SRC, severe and acute arterial hypertension develops due to the narrowing of renal vessels, which reduces the GFR. This further increases the production of angiotensin II. Persistent high blood pressure can lead to nephrosclerosis and chronic kidney failure. Kidney involvement in SSc can manifest in several forms: 1. SRC – This is one of the most severe and life-threatening complications of SSc, characterized by sudden onset of severe arterial hypertension, rapidly progressing kidney failure, microangiopathic hemolytic anemia, and thrombocytopenia. 2. CKD – This develops gradually and is related to fibrosis of the renal vessels, typically observed in patients with a long history of SSc. Clinical signs include: fatigue and weakness, swelling in the feet and hands, dry and itchy skin, decreased appetite, nausea, proteinuria, arterial hypertension, osteoporosis, and bone pain (due to impaired kidney function). This condition generally progresses slowly over the years and leads to nephrosclerosis. Management includes controlling blood pressure, using ACE inhibitors to reduce proteinuria, monitoring kidney function, and considering dialysis or kidney transplantation [11]. Proteinuria and Nephrotic Syndrome are less common manifestations. Proteinuria refers to the excretion of high amounts of protein in the urine, indicating dysfunction of the kidney filtration system. If proteinuria is very high (> 3.5 g/day), it is called Nephrotic Syndrome. Nephrotic Syndrome is characterized by significant protein loss due to damage to the kidney glomeruli, leading to edema and metabolic disturbances. Main Symptoms of Nephrotic Syndrome: Proteinuria > 3.5 g/day. Hypoalbuminemia (< 30 g/L). Diffuse edema (fluid accumulation in the face, feet, and abdominal cavity). Hyperlipidemia (elevated cholesterol and triglyceride levels). Fat droplets and hyaline casts in the urine. Primary Causes: Minimal Change Disease (common in children). Focal segmental glomerulosclerosis (FSGS). Membranous Nephropathy. Diabetic nephropathy Amyloidosis and systemic autoimmune diseases (such as SLE and SSc) [12].

Diagnosis

The diagnosis of kidney damage in SSc includes several tests and evaluations. The frequency of renal crisis development in patients with SSc is assessed through various subjective, anamnestical, and objective clinical criteria, including: Urinalysis: Zimnitsky test, nechiporenko test, and general urine protein levels. Renal Function Tests: blood urea nitrogen (BUN), creatinine, and uric acid levels are measured. Autoantibodies: Testing for scleroderma-specific antibodies such as Scl-70, anticentromere antibodies. Other laboratory tests: Increased residual nitrogen and its components (urea, creatinine, uric acid), decreased glomerular filtration rate (GFR), proteinuria, and microangiopathic anemia are assessed. These tests help in the evaluation and monitoring of kidney function in patients with systemic sclerosis. Immunological Tests: Antinuclear Antibodies (ANA): Specific to SSc. Anti-topoisomerase I (Scl-70) and Anti-RNA Polymerase III Antibodies: Found in severe forms of SSc. Complement System (C3, C4): Can sometimes be decreased. Anti-RNA Polymerase III and antinuclear antibodies: Their presence can indicate the severity and progression of the disease [5, 8].

Instrumental Methods

Electrocardiogram and Radiography (excretory urogra¬phy of joints). Kidney Ultrasound: Used to examine kidney shrinkage, fibrosis, and impaired blood flow. Doppler Ultrasound of Renal Vessels: Detects narrowing or changes in renal arteries. Kidney Biopsy: Rarely performed, but can be used to assess microangiopathy and fibrosis of glomeruli, confirm SRC or other nephropathies in complex cases [11,12].

Modern Approaches to treatment

the main goal of treatment is to preserve kidney function, control blood pressure, and slow down the fibrotic processes. SRC is a life-threatening condition characterized by severe arterial hypertension and kidney failure. If treatment is delayed, the risk of dialysis or death increases.

1. Hypertensive Therapy. ACE Inhibitors (ACEI) – First-line treatment. Captopril, Enalapril, Lisinopril. These medications block the renin-angiotensin system, reducing blood pressure within the kidneys. They are fundamental for treating pulmonary heart disease, improving prognosis, and reducing mortality. ACE inhibitors should be started immediately upon the onset of SRC.

2. Calcium Channel Blockers (Amlodipine, Nifedipine). If ACE inhibitors are insufficient, calcium channel blockers are used to further reduce blood pressure.

3. Diuretics (Furosemide, Spironolactone). Used to

reduce edema and fluid retention. Caution is required if GFR <30 ml/min.

4. Statins (Atorvastatin, Rosuvastatin). Used to reduce hyperlipidemia and lower cardiovascular risk.

5. Immunomodulatory and Antifibrotic Therapy Since SSc is an autoimmune disease, immunomodulatory drugs are key in treatment. Rituximab (anti-CD20 monoclonal antibodies): Suppresses the immune system by depleting B lymphocytes, which helps reduce fibroblast activity and fibrosis. Mycophenolate Mofetil (MMF) – An immunosuppressive and antifibrotic drug that can help prevent kidney damage. Cyclophosphamide – Used in severe autoimmune diseases but has a risk of nephrotoxicity. Corticosteroids – Used cautiously in SSc as high doses can increase vasospasm and worsen the condition. Tocilizumab – An IL-6 inhibitor used in resistant forms of the disease.

6. Antifibrotic Therapy – Since SSc involves fibroblast activation and collagen accumulation, antifibrotic medications play an essential role in treatment. Nintedanib – An antifibrotic and antiangiogenic agent that can slow down kidney fibrosis. Pirfenidone – Reduces collagen synthesis and helps stop the proliferation of fibroblasts. Angiotensin-converting enzyme inhibitors (ACEIs) – One of the most effective drugs for preventing SRC and providing antifibrotic effects (e.g., captopril, enalapril) [7, 11].

7. Additional Approaches: Endothelin receptor antagonists (bosentan, ambrisentan) – Used to dilate blood vessels and reduce fibroblast activity. Antithrombotic and anticoagulant drugs – Used to prevent microthrombosis. Hypertension management – blood pressure control using ACE inhibitors or angiotensin receptor blockers [13].

Chronic Kidney Disease Treatment

Treatment of SRC and CKD focuses on controlling blood pressure, preventing further fibrosis, and improving kidney function monitoring. Treatment Principles: 1. Blood Pressure Control: ACEIs or angiotensin receptor blockers (ARBs) are the first choice for treatment (e.g., captopril, enalapril). These medications dilate renal blood vessels, lower blood pressure, and slow the progression of kidney failure. 2. Caution with Steroids:

High doses of steroids (e.g., prednisone) can trigger SRC, so their use should be restricted. 3.Support Kidney Function: Maintain sodium and fluid balance. Low-sodium (salt-free) and low-protein diet. Monitor potassium levels. 4. Dialysis or Kidney Transplantation: If the disease reaches its final stages, hemodialysis or peritoneal dialysis may be required. In some cases, kidney transplantation may also be considered. 5.Treat the underlying Cause: Address the primary cause of the disease to prevent further complications. Immunosuppressive Medications for SSc: Immunosuppressive drugs (such as mycophenolate mofetil, cyclophosphamide) may be prescribed for SSc. Immunosuppressive Therapy: To reduce the activity of SSc, immunosuppressive medications like azathioprine, methotrexate, and mycophenolate are used [1, 8].

Complications

Monitoring blood pressure and adhering to a sodium-restricted diet. ACE inhibitors or angiotensin receptor blockers (ARB) are helpful in lowering blood pressure and reducing proteinuria [12]. Treatment of Complications: Anemia: Treated with erythropoietin and iron supplements. Electrolyte Imbalances: Appropriate medications are used to treat conditions like hyperphosphatemia or hyperkalemia.

Prognosis and Outcomes: The prognosis for kidney damage depends on early diagnosis and treatment. Without therapy, SRC is associated with a high mortality rate, but using ACE inhibitors significantly improves survival. CKD develops slowly, but continuous monitoring and treatment are required.

CONCLUSION

Kidney damage in SSc remains a serious issue that requires a comprehensive approach. Chronic kidney failure in systemic sclerosis primarily develops due to vascular damage, fibrinoid necrosis, fibroblast activation, and immune mechanisms. In particular, SRC progresses rapidly and can lead to acute kidney failure. Early diagnosis, blood pressure control, attention to laboratory indicators, and immunosuppressive therapy are essential to slow the progression of CKD and improve the overall condition of the patient. The pathogenesis of SRC is linked to microangiopathy and excessive activation of the RAAS. Effective treatment measures can help improve quality of life and prevent the development of kidney failure. Modern treatment methods may improve prognosis; however, further research in antifibrotic therapy and individualized patient care is needed.

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