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Review Article

# Renal Involvement in Rheumatic Diseases

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Most rheumatic diseases are chronic inflammatory diseases. Kidney-related symptoms of rheumatic diseases are often present, which increase mortality and morbidity of patients with rheumatic diseases. When patients with rheumatic diseases show signs or symptoms of renal involvement, management for primary rheumatic diseases should be more aggressive. In general, the risk and severity of renal involvement in patients with rheumatic diseases depend on the type of primary rheumatic diseases. Rheumatic disease itself, chronic use of immunosuppressive agents and non-steroidal anti-inflammatory drugs, and comorbidities, such as diabetes, hypertension, and cardiovascular complications, are the main causes of renal involvement in patients with rheumatic diseases. Many studies have reported the predominant features of renal involvement in most rheumatic diseases. We have attempted to summarize the relationships between rheumatic diseases and renal diseases, and clinical or pathophysiological features of renal involvement resulting from primary rheumatic diseases except systemic lupus erythematosus. Review for renal involvement, particularly in relation to early diagnosis and management of renal involvement in rheumatic diseases, is clinically significant because renal involvement in rheumatic diseases generally implies a bad prognosis. **(J Rheum Dis 2017;24:174-184)**

**Key Words.** Kidney diseases, Rheumatic diseases, Inflammation

## INTRODUCTION

Renal involvement in patients with several rheumatic diseases including rheumatoid arthritis (RA), systemic lupus erythematosus, and vasculitis is multifactorial. Most patients with chronic rheumatic diseases have comorbidities, such as diabetes mellitus, hypertension, and several cardiovascular diseases. These comorbidities are associated with the development of chronic kidney disease (CKD) and increased mortality resulting from the development of CKD, particularly in rheumatic diseases [1]. Chronic inflammation is a common pathophysiological mechanism of most rheumatic diseases and may result in the development of cardiovascular complications and CKD [2]. Chronic use of rheumatic drugs including non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate, bucillamine, and tumor necrosis factor-alpha (TNF-$\alpha$) inhibitor, can cause renal dysfunction by developing glomerulonephritis or tubulointerstitial nephritis (TIN) [3-6]. The factors, such as comorbidities, chronic inflammation, and long-term use of nephrotoxic drugs in patients with rheumatic diseases, are important in relation to renal involvement of rheumatic disease. In addition, the increase in human lifespan and harmful environmental factors associated with chronic inflammation results in increased comorbidities and the development of CKD in patients with rheumatic disease [7].

Renal involvement of rheumatic diseases clinically varies from severe glomerulonephritis to urinary abnormality without renal dysfunction. In detail, renal involvement of rheumatic diseases manifests in different forms of clinical manifestation, depending on which part of the nephron is predominantly involved. For example, patients with RA may have renal amyloidosis, which manifests by accumulating amyloid fibril mainly in glomeruli or tubulointerstitium. Renal involvement in systemic lu-

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pus erythematosus is expressed as lupus nephritis which mainly involves the glomeruli. TIN is mainly expressed in renal involvement of primary Sjögren's syndrome (pSS). Rapid progressive glomerulonephritis (RPGN) can be often expressed in patients with small vasculitis associated with antineutrophil cytoplasm antibody (ANCA) [8].

On the contrary, long-standing kidney diseases may cause rheumatic diseases, such as dialysis-related amyloidosis and gout. Dialysis-related amyloidosis mainly results from beta-2 microglobulin accumulation in several sites including bones, joints, and periarticular tissues. Chronic arthritis, such as degenerative osteoarthropathy, and spondyloarthropathy, occurs due to dialysis-related amyloidosis. Whether hyperuricemia itself is the cause of renal dysfunction remain unclear, but decreased urinary excretion of uric acid in patients with CKD and hyperuricemia resulting from it may lead to chronic gout [9]. Since the therapeutic approach to secondary rheumatic diseases differs from the treatment of primary rheumatic disease, the differential diagnosis of primary rheumatic diseases from secondary rheumatic diseases caused by CKD has a particularly great clinical significance in the diagnosis and treatment of chronic diseases.

In this review, we focused on the clinical or pathological features of renal involvement in patients with rheumatic diseases.

## MAIN SUBJECTS

### Renal involvement in RA

The prevalence of RA generally varies from 0.1% to 5% [7,10]. In contrast to systemic lupus erythematosus, renal involvement in RA is not frequent [11]. However, renal involvement in patients with RA is an important indicator of poor prognosis [12]. According to previous literature, the prevalence of renal involvement in patients with RA varies between 5% and 50% [12,13]. Renal involvement including glomerulonephritis and renal tubular dysfunction in RA often occurs due to chronic inflammation, which is the main pathophysiologic mechanism of RA. To date, the main causes of this renal involvement in RA were speculated as components such as chronic inflammatory disease itself or comorbidities resulting from chronic inflammation, and nephrotoxic drugs including DMARDs and NSAIDs, which are used for the management of chronic autoimmune inflammatory reaction. However, the chronic use of anti-rheumatic drugs rather than chronic inflammation itself of RA is the clinically more frequent cause of renal involvement in patients with RA [8]. Long use of DMARDs, such as methotrexate, leflunomide, and TNF-$\alpha$ inhibitor in RA may reduce the incidence of several comorbidities including cardiovascular diseases by effective control of chronic inflammation [14]. However, conventional drugs, including NSAIDs, methotrexate, and bucillamine, can often result in renal involvement, such as renal TIN, membranous nephropathy, and mesangial proliferative glomerulonephritis (mspGN) [11,12,15].

Regardless of the causes, renal abnormalities in patients with RA may be clinico-pathologically present as glomerular forms. These abnormalities include asymptomatic urinary abnormality, mspGN, membranous nephropathy, minimal change disease, renal amyloidosis, and even extra-capillary proliferative glomerulonephritis or TIN.

According to a previous literature, the frequency of glomerulonephritis and amyloidosis in RA is about 60% and 20%~30%, respectively. Chronic or acute TIN is not relatively frequent rather than the glomerular involvement [16]. Although the prevalence is different based on several studies, mspGN and membranous nephropathy are the most frequent types of renal involvement in patients with RA [11,12,15]. The most common feature of direct renal invasion is mspGN with mesangial infiltration of mainly immunoglobulin M and G although a direct renal involvement of RA is uncommon [17]. However, membranous nephropathy is mainly associated with chronic use of NSAIDs and previous DMARDs, particularly gold compounds, D-penicillamine rather than direct renal involvement of RA [16]. Renal amyloidosis is the most common pattern of renal involvement combined with decreased renal function in patients with RA [12]. By contrast, renal dysfunction is relatively less frequent in patients with RA and renal involvement such as membranous nephropathy and mspGN. Therefore, the development of renal amyloidosis in patients with RA increases morbidity and renal mortality and is a major cause of patients with RA requiring dialysis [12,16].

Proteinuria on urinalysis can be shown different according to the histologic pattern of renal involvement. Proteinuria caused by renal involvement, such as membranous nephropathy, mspGN, and minimal change disease, mainly consists of albuminuria. On the other hand, proteinuria composed of relatively low-molecular weight proteins, such as immunoglobulin, tubular protein, and light chain, is common in patients with RA combined with renal amyloidosis and TIN. Generally, dipstick test is

a basic diagnostic tool used to determine urinary abnormalities including proteinuria, hematuria, and pyuria. However, proteinuria composed of only other proteins without albumin cannot be identified by urinary dipstick test. Besides this false-negative reaction, false-positive reaction of dipstick test can also be shown in urinary dipstick test (Table 1). Thus, if proteinuria via urinary dipstick test is seen or suspected in patients with RA, rheumatologists or nephrologists consider quantitative urinary tests, such as 24-hour urinalysis, and spot urine protein-creatinine ratio (UPCR) or spot urine albumin-creatinine ratio (UACR). As previously mentioned, renal involvement in RA increases morbidity and mortality particularly in patients with RA [13]. However, renal involvement of RA may be present as urinary abnormalities (only proteinuria, only hematuria, proteinuria combined hematuria) without renal dysfunction. Therefore, periodic laboratory tests including urinalysis, serum creatinine, and electrolytes should be initially performed in patients with rheumatic diseases. If proteinuria is detected, quantitative urinalyses, such as 24-hour urinalysis, UPCR, and UACR should also be considered.

Managements of renal diseases in RA should be individualized according to the causes and clinical forms of renal involvement. In case of membranous nephropathy or mspGN due to nephrotoxic drugs, such as NSAIDs or DMARDs, avoiding or changing the offending drugs while carefully monitoring disease activity of RA should be attempted. Renal amyloidosis caused by RA usually presents with amyloid A amyloidosis rather than with light-chain amyloidosis. Since the development of renal amyloidosis shows a positive correlation with disease activity of RA, effective control of RA itself is important in the development and management of renal amyloidosis. If patients with RA show rapidly progressive renal dysfunction without a definite cause, such as nephrotoxic agents, renal biopsy should be considered. Although clinically rare, if crescentic glomerulonephritis or RPGN is confirmed by renal biopsy, the use of pulse-therapy of systemic steroid combined with immunosuppressants, including cyclophosphamide and rituximab, should be considered.

**Table 1.** Characteristics of urinary dipstick test

| Variable | Reagent strip method (dipstick test) |
|---|---|
| Principle | Tetrabromphenol, Semi-quantitative test |
| Detected protein | Mainly albumin |
| Sensitivity | Usually 10～30 mg/dL |
| Interpretation | Through color change of reagent strip |
| False positive reaction | Highly concentrated urine<br>Alkaline urine (urinary pH ＞8)<br>Radiographic contrast media<br>Blood in urine<br>Chlorhexidine or antiseptics |
| False negative reaction | Highly diluted urine<br>Immunoglobulins<br>Tamms-Horsefall mucoprotein (tubular protein)<br>Bence Jones proteins (light chains) |

## Renal involvement in pSS

pSS is a progressive autoimmune disease, which is mainly characterized by lymphocytic infiltration and malfunction of exocrine glands. The prevalence rate of this disease in women is 9 times higher than that of men [18]. However, the exact prevalence of pSS due to continuous changes in diagnostic guidelines and differentiation from secondary pSS is difficult to determine [19]. pSS can involve multiple organs including the kidney, joints, lungs, hematologic system, vascular system, and peripheral nervous system as well as exocrine glands [20].

The prevalence of reported renal involvement in patient with pSS ranges from 5% to 20% according to previous reports [20-23]. Renal involvement in patients with pSS is mainly reported in elderly rather than younger patients. The prognosis of the renal involvement of pSS is relatively good, and CKD progression is clinically rare [21,24].

The renal involvement of pSS can also be expressed in various forms, such as asymptomatic urinary abnormalities, renal tubular acidosis (RTA), Fanconi's syndrome, diabetic insipidus, renal calculi, glomerulonephritis, and TIN [20]. Similarly, the renal involvement of pSS is mainly composed of renal tubular dysfunction rather than glomerular dysfunction. According to most clinical or clinicopathological studies related to the renal involvement of pSS, TIN is the most common pathologic finding in the renal involvement of pSS. However, glomerulonephritis, such as membranoproliferative glomerulonephritis and membranous nephropathy, is usually less frequent in patients with pSS [20,21,24].

The symptoms and signs of TIN may not be clinically relevant. Microscopic hematuria and proteinuria rather than the clinical signs, such as azotemia, hypertension, and electrolytes imbalance, are well developed in TIN. In addition, an isolated proteinuria in TIN is difficult to detect with only urinary dipstick test because proteinuria

from the renal tubular injury is mainly composed of tubular proteins with small molecular weight than the relatively large albumin [20,25]. Thus, the renal involvement in pSS may be underdiagnosed. This underdiagnosis may be attributed to the limitation of the urinary dipstick test that only detects albumin rather than tubular proteins with small molecular weight.

According to several reports, renal tubular dysfunctions are primarily expressed in a distal RTA form in patients with pSS with histologically acute or chronic TIN [19-21,24]. Distal RTA is the most common acid-base disturbance with electrolyte imbalance particularly in the renal involvement of pSS. The distal RTA usually results from the impairment of urine acidification by reducting net hydrogen ion secretion on the collecting duct. Urine pH is generally over 5.5 due to an inability to acidify urine like mentioned above. Metabolic acidosis can result in decreased proximal fluid reabsorption, which eventually leads to volume contraction and activation of the renin-angiotensin-aldosterone system (RAAS). The increase in distal tubular sodium delivery and serum aldosterone by RASS activation and the decrease in proximal fluid reabsorption finally leads to hypokalemia. Beside hypokalemia, metabolic acidosis, and RASS activation, nephrolithiasis or hypercalciuria can be developed in patients with distal RTA by pSS [26]. The increase in urinary calcium excretion is mainly caused by bone buffering against persistent metabolic acidosis [27]. In addition, a previous literature showed that distal RTA is well correlated with the degree of hypergammaglobulinemia in pSS [24]. In comparison to distal RTA, proximal RTA, Fanconi's syndrome can develop in patients with pSS, but its incidence is relatively low. The most common presentation of pSS is TIN, which is clinically expressed as signs including hypokalemia, hypercalciuria, and metabolic acidosis, similar to previous mentioned. However, the relationship between renal dysfunction and the clinical signs remains unclear [20].

If the renal involvements of pSS present with clinical signs, such as severe electrolytes imbalance, and significant renal dysfunction, a renal biopsy should be performed to evaluate a possibility of treatment and overall prognosis [20,21]. An identification of the chronicity and severity of renal tubulointerstitial inflammation through renal biopsy will facilitate to determine the therapeutic effect of steroid-based immunosuppressants and the prognosis of the overall disease.

The best treatment option of TIN in patients with pSS is corticosteroids. The initial dose of corticosteroids usually ranges from 30 mg to 60 mg (approximately $\geq$0.5 mg/kg of corticosteroid per day) [20,21]. If patients with TIN combined with glomerulonephritis, other immunosuppressants, such as cyclophosphamide, mycophenolate mofetil, and rituximab, can be added according to specific findings of renal biopsy [21].

The response of first-line therapy, corticosteroid for TIN in patients with pSS according to previous retrospective studies is very good [21,24]. No progression to end-stage renal disease (ESRD) was found in most patients with TIN and pSS, which were adequately treated with corticosteroids or other immunosuppressants.

In summary, the renal prognosis in patients with renal involvement, such as TIN, glomerulonephritis, and tubular dysfunction caused by pSS, is relatively good. However, the chronicity and severity of TIN, including severe infiltration of inflammatory cells, interstitial fibrotic changes, and tubular atrophy, should also be considered. The prevalence of renal involvement in patients with pSS ranges from 5% to 20%, but prompt and adequate treatments in patients with pSS with renal involvement are important for renal prognosis. Therefore, rheumatologists or nephrologists should perform adequate screening tests, including quantitative urinalysis via 24-hour urine collection, urinary pH and osmolarity, serum creatinine, serum bicarbonate, serum potassium, and serum phosphate at least twice a year in patients with pSS who are suspected with renal involvement (Table 2) [20]. In addition, if signs of renal involvement are evident, renal biopsy should be immediately considered.

## Renal involvement in ANCA-associated vasculitis

The kidney is a main target organ of systemic vasculitis. A renal vasculitis can manifest in one form of the following disease entities: immunoglobulin A vasculitis (Henoch-Schönlein purpura nephritis), cryoglobulinemic vasculitis, and pauci-immune vasculitis mainly involved small-sized vessels. The clinical manifestations of systemic vasculitis usually present with nonspecific symptoms or signs, such as fever, chills, malaise, myalgia, generalized weakness, and arthralgia. The manifestations can also vary depending on involved tissue, disease activity, and disease severity [28]. Small-sized vessel pauci-immune vasculitis is usually related to autoantibodies, such as myeloperoxidase (MPO) or proteinase 3 (PR3)–ANCA [29]. The diagnosis and classification of ANCA-associated vasculitides (AAV) has been continuously developed, and classification is mainly based on histology and

**Table 2.** Renal screening tests in patients with primary Sjögren's syndrome

| Variable | Every 6 months in pSS patients with renal abnormalities | Every 1 year in all pSS patients |
|---|---|---|
| Urinalysis | Dipstick test: urine pH, osmolality, glycosuria<br>24 hour urinalysis: protein, albumin, creatinine, citrate, calcium, culture | Dipstick: urine pH, osmolality, glycosuria<br>UPCR, UACR |
| Serologic tests | Creatinine, potassium, chloride, bicarbonate, calcium, phosphate, uric acid | Creatinine, potassium, chloride, bicarbonate |
| Imaging tests | Kidney ultrasonography | - |

pSS: primary Sjögren's syndrome, UPCR: spot urine protein to creatinine ratio, UACR: spot urine albumin to creatinine ratio, -: none.

**Table 3.** Frequency of systemic involvement in ANCA-associated small vessel vasculitis

| Systemic organ | Frequency of involvement | | |
|---|---|---|---|
| | MPA | GPA | EGPA |
| Kidney | 90 | 80 | 45 |
| Skin | 40 | 40 | 50 |
| Lung | 50 | 90 | 90 |
| ENT | 35 | 90 | 50 |
| Musculoskeletal | 60 | 60 | 50 |
| Neurologic | 30 | 50 | 60 |

Values are presented as percentage. ANCA: antineutrophil cytoplasm antibody, MPA: microscopic polyangiitis, GPA: granulomatosis with polyangiits (Wegener's), EGPA: eosinophilic granulomatosis with polyangiits, ENT: ear, nose, throat.

clinical manifestation. According to Chapel Hill Consensus Conference in 2012 [30], AAV is mainly composed of microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA). According to a previous literature [31], ANCA positivities of AAV were about 60% in GPA and about 5% to 8% in EGPA. ANCA positivity of MPA was prominently higher compared with other vasculitis (approximately 70% to 90%).

Renal involvement of AAV is frequently observed and also reflects a poor prognostic factor for mortality and morbidity [29,31]. Renal involvement occurs more frequently in GPA and MPA compared to in EGPA (Table 3) [32]. We can clinically recognize the presence of renal involvement of AAV by identifying hematuria, proteinuria, azotemia, edema, and hypertensive symptoms [30]. Although glomerular filtration rate (GFR) at onset time of renal vasculitis associated with AAV reflects a renal outcome, renal histologic feature is also an important predictor for disease outcome particularly in the renal vasculitis associated with AAV [29,33].

In a histologic sense, severity of acute lesions, such as glomerular crescents and fibrinoid necrosis, rather than chronic lesion-like glomerular sclerosis is well correlated with renal outcome and responsiveness of immunosuppressants in several renal vasculitides associated with AAV [29,33,34]. Classification of ANCA-associated glomerulonephritis based on renal biopsy results has been developed for the prognosis of renal vasculitis [29,33,34]. 'Focal' lesion represents a relatively preserved renal function and 'crescentic' lesion shows a good responsiveness for immunosuppressant therapy. 'Mixed' and 'sclerotic' lesions represent intermediate and high risks of aggravation of renal function, respectively (Table 4) [29,34]. Tubular atrophy and interstitial fibrosis are well-known indicators of poor prognosis for all of renal diseases. In addition to glomerulonephritis, interstitial nephritis and tubular damages, such as tubulitis and tubular atrophy, may also be seen in renal involvement of AAV. The tubular inflammation in ANCA-associated renal vasculitis can be associated with inflammatory cells such as CD4 positive T-cells [29,35]. Thus, T and B cell target therapies may also be used in the treatment of ANCA-associated renal vasculitis. The activation of alternative complement pathway can also be related to pathological mechanism of AAV according to a previous study [36].

Clinically, vasculitis may occur even if the serum level of ANCA is the normal range, and this serum level is not correlate with disease activity or severity of vasculitis. There is also a similar relationship for ANCA-associated renal vasculitis. As mentioned earlier, the renal outcome of ANCA-associated renal vasculitis is mainly related to GFR at onset time of renal disease and specific pathologic findings including several glomerular damages, interstitial fibrosis, and tubular atrophy rather than the serum ANCA level. However, according to several studies

[33,34,37], less severe pathological involvement, such as focal class, is mainly shown in patients with PR3-ANCA-associated renal vasculitis than in patients with MPO-ANCA-associated renal vasculitis. ANCA type rather than serum titer may be an important factor of treatment response. For example, patients with MPO-ANCA-associated renal vasculitis have much poorer renal outcome than those with PR3-ANCA-associated renal vasculitis [33,34,37].

The treatment of ANCA-associated renal vasculitis is mainly composed of high-dose glucocorticoid and systemic cyclophosphamide for three months or six months in induction therapy. Several randomized controlled trials for the treatment of AAV have been performed over the past several decades, and systemic immunosuppressants, such as cyclophosphamide, methotrexate, and rituximab combined with high-dose glucocorticoid, are very effective drugs in induction therapy, particularly for controlling acute inflammation (Table 5) [29]. Among these immunosuppressants, methotrexate should not be used in patients with decreased GFR. After the induction therapy, maintenance therapy with low-dose glucocorticoid combined with azathioprine or methotrexate should be also continued to prevent relapse. Clinically, the duration of induction therapy and the intensity of maintenance therapy should be decreased as much as possible to reduce toxic side effects. We can use the intravenous cyclophosphamide rather than oral cyclophosphamide to reduce drug toxicity, such as leukopenia and bladder cancer. However, we need to recognize that long-term follow-up demonstrates longer time to relapse in the oral cyclophosphamide-treated group [38].

In addition, plasma exchange may be a good option in patients with life-threatening pulmonary hemorrhage or severe renal disease which emergent dialysis is needed [29,39,40]. However, plasma exchange did not result in increase of survival rate, especially in patients with severe renal disease due to ANCA-associated renal vasculitis [41]. Recently, several studies have been continued for newer therapeutic agents, including bortezomib (proteasome inhibitor), gusperimus, and alemtuzumab (anti-CD52 pan lymphocyte-depleting antibody), to manage AAV effectively [29].

In conclusion, treatment of ANCA-associated renal vasculitis is largely composed of induction and maintenance therapies, and effective immunosuppressants can be chosen according to disease severity (Figure 1) [32].

**Table 4.** Classification for ANCA-associated glomerulonephritis

| Class | Inclusion criteria |
|---|---|
| Focal | > 50% normal glomeruli |
| Crescentic | > 50% glomeruli with cellular crescents |
| Mixed | < 50% normal, < 50% crescentic, and < 50% globally sclerotic glomeruli |
| Sclerotic | > 50% globally sclerotic glomeruli |

ANCA: antineutrophil cytoplasm antibody.

## Renal involvement associated with systemic sclerosis

Systemic sclerosis (SSc) is a rare connective tissue disease even if the prevalence is quite different according to country or area [42]. SSc consists of limited and diffuse systemic sclerosis. It is mainly characterized by vasculopathy that involves from peripheral to renal vessels and fibrotic change of connective tissue by chronic autoimmune reaction.

Renal involvement caused by SSc can clinically vary from mild urinary abnormality without renal dysfunction to systemic renal crisis (SRC). Patients with renal involvement of SSc often show a decreased GFR. However, mild-to-moderate renal impairment (GFR < 90 mL/min/1.73 $m^2$ and GFR < 60 mL/min/1.73 $m^2$, respectively)

**Table 5.** Several randomized controlled trials (RCTs) in treatment of ANCA-associated vasculitis

| RCT | Induction | Maintenance | Result |
|---|---|---|---|
| CYCLOPS | IV-CY + steroid vs. Oral-CY + steroid | AZA + steroid | Similar efficacy |
| RITUXVAS | RTX + IV-CY* + steroid vs. IV-CY* + steroid | AZA + steroid | Similar efficacy |
| RAVE | RTX + steroid vs. Oral-CY + steroid | AZA | Similar efficacy |
| NORAM | MTX + steroid vs. Oral-CY + steroid | MTX/Oral-CY + steroid | MTX: less effective |
| IMPROVE | Oral-CY + steroid | MMF + steroid vs. AZA + steroid | MMF: less effective |
| WEGENT | IV-CY + steroid | MTX + steroid vs. AZA + steroid | Similar efficacy |

ANCA: anti-neutrophilic cytoplasmic antibody, IV: intravenous, CY: cyclophosphamide, AZA: azathioprine, RTX: rituximab, MTX: methotrexate, MMF: mycophenolate mofetil. *Low-dose cyclophosphamide (2 doses).

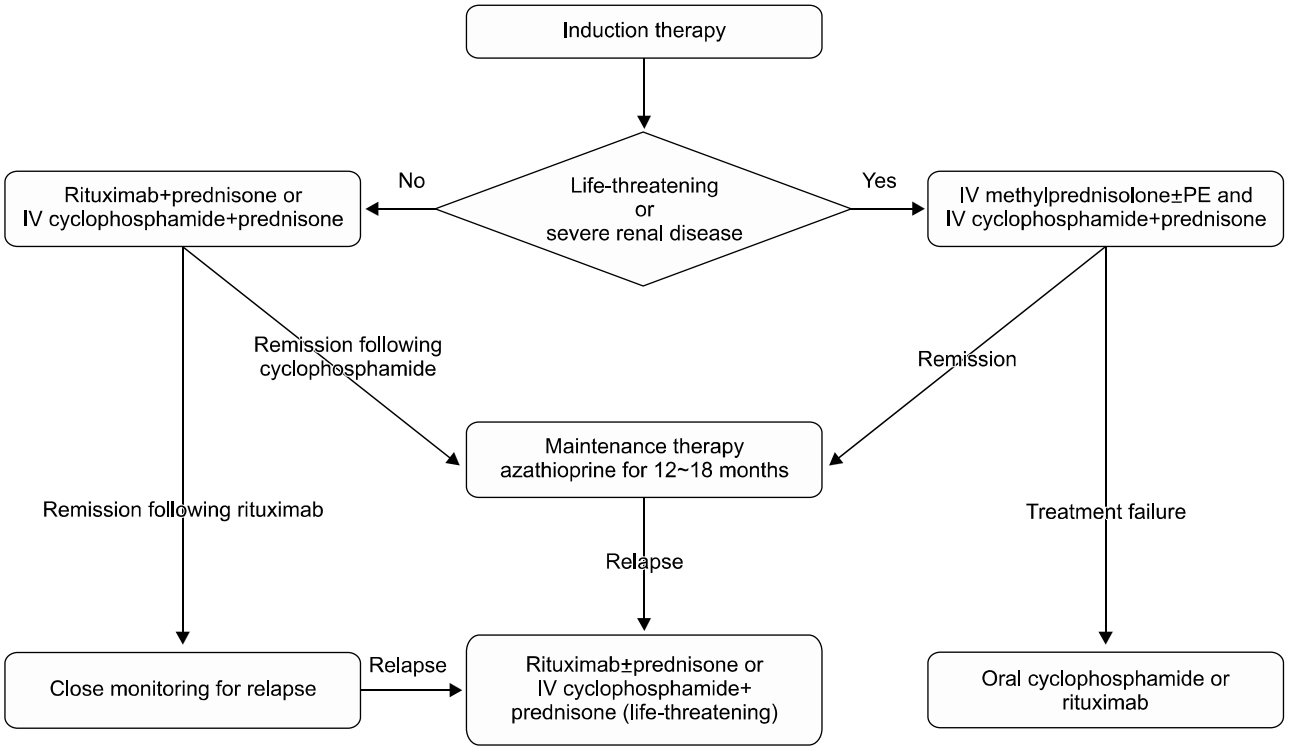


**Figure 1.** Treatment of ANCA-associated renal vasculitis. IV methylprednisolone usually begins with 7 mg/kg per day of methylprednisolone for 3 days and followed by oral prednisone 1 mg/kg per day. IV cyclophosphamide usually begins with 0.5 g/m$^2$ per monthly of cyclophosphamide. Oral cyclophosphamide usually begins with 2 mg/kg per day of cyclophosphamide and the dose can be reduced based on renal function or age. Oral prednisone should be tapered slowly during 3 to 6 months. Oral azathioprine usually begin with 2 mg/kg per day of azathioprine. ANCA: anti-neutrophilic cytoplasmic antibody, IV: intravenous, PE: plasma exchange.

usually occurs more frequently than severe renal dysfunction (GFR $<$30 mL/min/1.73 m$^2$) or ESRD [43].

SRC is a clinical condition accompanied by malignant hypertension and acute renal dysfunction in SSc. The SRC occurs in less than about 5% of patients with mainly diffuse SSc, but it is the most serious complication among renal involvement of SSc [42,44,45]. The pathogenesis of SRC has not been elucidated [42]. However, a specific vascular lesion-like "onion-skin" and luminal narrowing resulting from intimal and medial proliferation of renal vessels, such as arcuate and interlobular arteries on histopathology, show a significant relationship between SRC and renal vasculopathy. A progressive systemic sclerosis may often occur in ischemic nephropathy such as renal infarction and subcapsular hemorrhage [46]. In addition, patients with SRC or renal dysfunction related to SSc usually show decreased blood flow.

Clinically, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) is commonly used because the vascular change and activation of the RAAS caused by decreased renal blood flow in patients with SSc with renal involvement. Whether the use of ACEI may be associated with reduced GFR in patients with SSc is not certain. Thus, using ACEI or ARB is generally better in patients with SSc, even if they have renal insufficiency [42,46]. On the contrary, hypovolemic conditions caused by several risk factors including sepsis, congestive heart failure, cardiac arrhythmia, and dehydration and drugs, such as cyclosporin, corticosteroid, and NSAIDs, are triggering factors of SRC. According to several studies, corticosteroid can increase the serum levels of endothelin-1 and endothelin receptors [42,47,48]. The effects of corticosteroid on several factors, such as prostacyclin, blood pressure, and volume, are also related to aggravation of SRC caused by corticosteroid use. However, determining whether the cause of renal dysfunction in patients with SSc is due to the development of SRC or acute kidney injury caused by the aforementioned risk factors is clinically difficult. Clinical signs or symptoms related to renal involvement of SSc may be often absent. Therefore, rheumatologists and nephrologists should attempt to identify the triggering factors or causa-

tive factors.

Laboratory data, such as proteinuria, microscopic hematuria, hemolytic anemia, thrombocytopenia, and antinuclear antibodies including anti-RNA polymerase III antibodies, may be also helpful for SRC diagnosis. A previous cohort study revealed that anti-RNA polymerase III antibodies are positively correlated with the development of SRC [49]. There is also a report that anti-RNA polymerase III antibody is closely associated with renal insufficiency and diffuse SSc [42]. However, a comprehensive consideration of clinicopathological factors should be given with regard to the definite diagnosis of SRC. In Korea, SRC is very rare, and SRC related with anti-RNA polymerase III antibody is also extremely rare [50]. In general, SRC shows the following symptoms or signs including severe hypertension accompanied by neurologic symptoms, acute renal dysfunction, thrombotic microangiopathy, proteinuria, and microscopic hematuria. Renal biopsy is often not required in clinical situations where SRC is suspected, but it should be considered when an aggressive deterioration of renal function or atypical renal manifestation by SSc is present [42].

Early diagnosis and management of SRC in patients with SSc is very important. When renal involvement of SSc is suspected, glucocorticoid use should be firstly discarded. As previously mentioned, high-dose corticosteroid (>15 mg/day of prednisolone) may be a triggering factor of SRC because the characteristics of corticosteroid influence several factors such as endothelin, prostacyclin, and blood volume or pressure [51]. In addition, ACEI or ARB is the main drug used for the renal involvement of SSc including SRC. The use of ACEI is better to be continued in patients undergoing dialysis or not and in those who recovered from renal function and has hypertension. Besides ACEI or ARB, anti-hypertensive agents, such as calcium channel blockers, minoxidil, and prazocin, can be added to control hypertension adequately, but beta blockers should be avoided. As for the relationship between endothelin and SRC, endothelin receptor blockers may be considered in SRC. However, a large study or a randomized control study about the use of endothelin receptor blockers for SRC is needed [42]. When patients with renal involvement of SSc have uremic symptoms or signs, physicians should consider emergent dialysis. Dialysis is usually required about half of patients with SRC according to a previous report [42].

## Renal involvement associated with gout or hyperuricemia

A long-standing hyperuricemic condition may lead to progressive formation of uric acid crystal within renal tubules, which may result in CKD. According to previous studies, hyperuricemia itself may be associated with several pathologies such as metabolic syndrome, afferent arteriolopathy of kidney, activation of RAAS, and endothelial dysfunction characterized by inhibition of nitric oxide system [9,52-54].

These factors, caused by hyperuricemia itself, lead to renal involvement, such as acute TIN, and ischemic nephropathy and eventually lead to progression to CKD. On the contrary, Latif et al. [55] reported that the antioxidant effect of uric acid may decrease all-cause mortality and cardiovascular mortality in patients with ESRD requiring dialysis. Therefore, the causal relationship between hyperuricemia itself and renal dysfunction has been not definitely clarified. In addition, clinical factors, such as hypertension associated with hyperuricemia, nephrotoxic drugs such as NSAIDs in patients with gout and hyperurmicemia, and underlying vasculopathy in hyperuricemic patients can influence the reduction of renal function [9].

The prevalence of renal involvement in patients with gout is relatively high. In particular, the prevalence of hypertension or moderate CKD (lesser than GFR <60 mL/min) in patients with gout was reported to be over 70% by Zhu et al. [56]. In addition, CKD patients including ESRD patients undergoing dialysis may also often experience gout. Thus, the relationship between gout and renal involvement is bi-directional.

Clinically, the therapeutic target of serum uric acid level in gout patients regardless of CKD is below 6 mg/dL. For the appropriate reduction of serum uric acid in patients with gout, many physicians use xanthine oxidase inhibitors, such as allopurinol and febuxostat. However, the use of allopurinol in CKD patients requires considerable care. In particular, allopurinol hypersensitivity syndrome, characterized by symptoms or signs such as skin rash, anaphylactic reaction, Stevens-Johnson syndrome, toxic epidermal necroloysis, and multi-organ dysfunction may be easily developed in patients with CKD. However, febuxostat has a relatively low incidence of adverse effects compared to allopurinol and its use is relatively flexible even in patients with renal dysfunction. So, many nephrologists and rheumatologists prefer febuxostat rather than allopurinol [57].

The use of xanthine oxidase inhibitor and colchicine in

patients with CKD and gout has been debated. However, in patients with advanced CKD, administration of 50 mg/day allopurinol is better, and the dose of the drug should be gradually increased to maintain the target level of serum uric acid. Colchicine should be also started with 50% dose reduction and continued for 3 to 6 months after achieving the target level of serum uric acid depending on the presence or absence of tophi [9,58,59].

### Renal involvement associated with nephrotoxic for control of rheumatic diseases

Since most rheumatic diseases are not curable and require the use of anti-inflammatory drugs for a long time, therapeutic drugs, such as NSAIDs, DMARDs, and even biologic agents, may often influence renal dysfunction or renal involvement in rheumatic patients. NSAIDs are mainly associated with renal involvement, such as acute TIN, and minimal change disease. In addition, NSAIDs contract the afferent arteriole of the kidneys by inhibiting prostaglandin production. The influence on renal vasculature of NSAIDs can result in decreased GFR. According to few reports, NSAIDs worsen renal function in patients with advanced renal dysfunction (estimated GFR $<30$ mL/min/1.73 $m^2$), but they do not show adverse effects in patients with normal renal function [5,7].

Recently, previous DMARDs such as gold compounds and D-penicillamine, are rarely used. However, conventional DMARDs including methotrexate, sulfasalazine, and lefunomide are widely used in patients with RA to manage chronic inflammation. The nephrotoxicity of these drugs is relatively less than the previous DMARDs mainly resulting in membranous nephropathy. However, conventional DMARDs should also be used cautiously according to the elimination rate of each drug by the kidneys [8,60].

Biologic agents, such as TNF-$\alpha$ blockers (adalimumab and etanercept), can also result in membranous nephropathy or proliferative glomerulonephritis accompanied by proteinuria via direct invasion of glomerular visceral epithelial layer [8]. Thus, when biologic DMARDs or conventional DMARDs are used in rheumatic diseases including RA, a renal surveillance should be regularly performed by rheumatologists or nephrologists.

In conclusion, kidney-related diseases related to anti-rheumatic drugs, including NSAIDs and DMARDs, are mainly composed of glomerulonephritis such as membranous nephropathy and TIN.

## CONCLUSION

Kidney diseases and rheumatic diseases demonstrates a close relationship. They can act as causative factors of each other. In particular, renal manifestation or renal involvement of rheumatic diseases is clinically significant because of the increase in mortality and morbidity in rheumatic patients with renal dysfunction.

Thus, early diagnosis and proper management of renal involvement in rheumatic diseases may improve overall or renal prognosis of rheumatic patients. The clinical and histologic manifestations of renal involvement in rheumatic diseases were investigated throughout this review. Renal involvement can be caused by anti-rheumatic drugs and rheumatic diseases. RA mainly induces glomerulonephritis, such as membranous nephropathy, mspGN, and amyloidosis. pSS induces tubular dysfunction including TIN and RTA. In addition, ANCA-associated vasculitis mainly induces RPGN accompanied by acute renal dysfunction. SSc is a relatively rare disease, but renal involvement of SSc including SRC may be fatal in view of renal prognosis. In relatively frequent patients with gout, renal involvement may be related to hyperuricemia.

In conclusion, a more effective approach for a definite diagnosis and proper care of rheumatic diseases can be achieved by accurately grasping the clinical characteristics of renal involvement in various rheumatic diseases.

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## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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