Renal Manifestations of Rheumatoid Arthritis

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KEYWORDS

• Rheumatoid arthritis • RA • Rheumatoid nephropathy • Rheumatoid kidney
• RA glomerulonephritis • Chronic kidney disease in RA • DMARDs in CKD

KEY POINTS

- Renal manifestations in patients with rheumatoid arthritis (RA) have evolved as management of RA has improved.
- Older disease-modifying antirheumatic drugs, uncontrolled systemic inflammation, and chronic nonsteroidal antiinflammatory drug (NSAID) use contributed to kidney disease in the past.
- The increased use of methotrexate and biologic medications, decrease in chronic NSAID use, and a treat-to-target strategy has contributed to a decrease in renal manifestations.
- Chronic kidney disease in patients with RA is now more closely associated with cardiovascular risk factors than with RA disease severity.
- In patients with established chronic kidney disease, medications such as NSAIDs, methotrexate, and tofacitinib may need to be adjusted or avoided to prevent adverse events.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease that primarily causes inflammation of the joints. The prevalence of RA is 1%, with a greater predominance in women.[1] Chronic inflammation in RA can result in joint destruction and significant physical disability, as well as premature cardiovascular disease (CVD).[2,3]

Renal manifestations can be seen in RA but have become less prevalent as medical therapies for treating RA evolved. Historically, the primary cause of renal insufficiency in patients with RA was nephrotoxicity of therapies for RA, such as nonsteroidal antiinflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs),

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such as penicillamine, bucillamine, gold, and cyclosporine. Poorly controlled systemic inflammation also led to mesangial proliferative glomerulonephritis (GN) or secondary amyloidosis. The emergence of methotrexate and targeted biologic agents, coupled with treat-to-target therapeutic approaches, marked a revolutionary turning point in the treatment of RA and greatly ameliorated the long-term consequences of chronic systemic inflammation and the need for older, more nephrotoxic DMARDs. In Asian nations, such as Japan and Korea, where older DMARD use is still common, medication-associated renal complications in patients with RA are still reported.

THE PREMETHOTREXATE AND PRE–TARGETED BIOLOGIC ERA

Prevalence of Renal Involvement in Rheumatoid Arthritis

In the era before methotrexate and targeted biologics, chronic kidney disease (CKD) was common in patients with RA, with a prevalence of 37% to 57%.[4,5] In contrast with systemic lupus erythematosus (SLE), clinically significant renal damage directly related to RA is typically not observed, except in the case of patients with poorly controlled disease activity who may develop secondary amyloidosis, which can lead to end-stage renal disease (ESRD).[6]

Most reports of CKD in patients with RA in more recent decades are in Asian populations, which may be attributed to differences in specific DMARD usage. RA medications that continue to be used in Asian nations such as Japan, Korea, and China, but are now rarely used in Western nations, include azathioprine, gold, bucillamine, cyclophosphamide, cyclosporine, and mycophenolate mofetil.[7,8]

Types of Renal Involvement in Rheumatoid Arthritis

Multiple regions of the kidney can be affected by RA and/or by treatment with RA medications. These regions include the glomerulus, vasculature, tubules, and the interstitium (**Box 1**). The level of proteinuria, active urinary sediment, and clinical symptoms do not accurately predict the renal histology in RA. Therefore, if unexplained CKD or proteinuria is detected, a renal biopsy is necessary for diagnosis.[6]

Glomerulonephritis

Autopsy studies in patients with RA describe mesangial proliferative, membranous GN, and crescentic GN, although there was little to no associated compromise in renal function reported.[9] Sub–nephrotic-range proteinuria is common in membranous GN and mesangial GN. Estimated glomerular filtration rate (eGFR), as defined by serum creatinine levels, was normal in most patients with RA who had mesangial and membranous GN.[6]

Mesangial glomerulonephritis The prevalence of mesangial GN ranges from 35% to 78% among patients with RA with known nephropathy.[6] It is usually associated with long-standing RA disease (12.9 $\pm$ 10.4 years).[6] However, it typically has a mild course and nephrotic syndrome and renal failure have only rarely been reported.[8] Interleukin (IL)-6, which is at increased levels in the peripheral blood and synovia of patients with RA, may be a growth factor for mesangial cells. In animal models, IL-6 induced proliferation of mesangial cells in the kidneys in a dose-dependent manner. In a small study by Horii and colleagues[10] of patients without RA who had primary mesangial proliferative GN, higher urine IL-6 levels were observed compared with patients with primary minimal change disease, primary membranous GN, and normal healthy controls. Whether chronically high levels of IL-6 cause mesangial GN in RA remains unclear.

Membranous glomerulonephritis Immune-complex deposition can occur in the glomerular basement membrane and lead to membranous GN. Immune-complex