Investigating Kidney Involvement in Rheumatoid Arthritis

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When it comes to renal involvement in connective tissue disease, the focus is on systemic lupus erythematosus (SLE). Affection of kidney in rheumatoid arthritis (RA) is more or less overlooked and mainly attributed to drugs viz. analgesics, non-steroidal anti-inflammatory drugs (NSAIDS) and disease modifying antirheumatic drugs (DMARDs) like gold and d-penicillamine which are less commonly used in today’s scenario. However, patient’s who have received gold and d-penicillamine in the past may still present in future with renal damage. The other major etiology of kidney involvement in RA is secondary amyloïdosis, commonly associated with long term disease process. Vasculitis associated with RA is relatively less common etiology of renal involvement. After ruling out the abovementioned etiologies, the RA patients with renal affection are labelled to have RA nephropathy.1

The diagnostic importance of the etiology of renal involvement in RA is self-explanatory as approach towards the management will differ with each.

The importance of studying kidney involvement in RA cannot be stressed more by noting observations made by Mutru et al2 who found renal diseases (especially amyloidosis) next only to infections and cardiovascular disease as main cause of mortality among 500 RA patients followed over a period of time. Boers et al3 noted among 35 patients with chronic, seropositive RA of which half had either vasculitis or hypergammaglobulinemia, decreased glomerular filtration rate in eight patients, proteinuria in 11, a defective urine concentration in 10 and increased urinary tubular enzyme levels in fifteen. They concluded that renal dysfunction can occur with almost same frequency in the absence of vasculitis and hypergammaglobulinemia in RA.

The various modalities to study renal involvement in RA include study of clinical manifestations and urinary abnormalities like haematuria, proteinuria, age-old ‘gold standard histopathology’ and glomerular and tubular proteinuria or other markers of nephropathy.

Creatinine clearance, the usually available simple test to assess renal function, lacks the sensitivity;5 whereas proteinuria is more sensitive to detect renal disease.6 Koreki et al8 concluded in their study that raised serum creatinine concentration or persistent proteinuria in patients with early RA is predominantly drug related whereas, in contrast, isolated haematuria is more directly associated with the activity of the disease process.

The prevalence of isolated microscopic haematuria in RA patient was not higher than that in control population as studied by Korpela et al.7 In the necropsy study by Boers et al the relationship between urine abnormalities and the renal function was not correlating, only 21% having urine abnormalities and loss of renal function. Vasculitis affecting kidneys in RA patient is known, however in an important observation by Harper et al it was found that only half the patients with renal vasculitis had extrarenal vasculitis as well. All the patients with renal vasculitis had proteinuria and focal segmental necrotising glomerulonephritis (FSNGN) and extracapillary proliferation. This observation should make one suspicious of renal vasculitis in proteinuric patients without evidence of any systemic vasculitis. Thus, in RA patient with urinary abnormality renal biopsy becomes mandatory.

Histopathology has always remained ‘gold standard’ to diagnose RA nephropathy. Yoshida et al9 studied 31 patients of RA with urinary abnormalities including seven with renal failure and found 16 patients had membranous nephropathy, two each had proliferative glomerulonephritis, glomerular abnormalities and tubulointerstitial nephritis and six had amyloidosis. Membranous glomerulonephritis (MGN) was related to gold or d-penicillamine intake (11 out of 16). In a larger study of 110 patient, Helin et al10 concluded that mesangial GN was associated more frequently with long standing RA than membranous GN, later was more likely to be drug-induced.

Nakano et al11 found mesangial GN and membranous GN as part of RA nephropathy in about two-thirds of the patients. Secondary amyloidosis was found in one-fifth. They also attributed thinning of glomerular basement membrane to RA itself. Korpela et al12 did not find any correlation of rheumatoid factor (RF), antinuclear antibody (ANA), circulating immune complex (CIC), C3 and C4 with mesangial glomerulopathy and amyloidosis. CIC did not have a major role in nephropathy unlike other extra-articular involvement in RA. Thus, the histopathology does not correlate with urinary abnormalities and serum markers of inflammation and immune process.

Traditionally the approach to detecting any renal disease has always been first the urinary examination followed by histopathological examination. Eventhough urinary examination is normal it does not exclude renal involvement.

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and kidney biopsy being invasive, cannot be done at regular interval to diagnose renal disease early, hence there is a need for resorting to other non-invasive investigating modalities.

Various markers are available to assess the status of renal injury. Serum creatinine and creatinine clearance lack sensitivity in detecting renal dysfunction especially in patients with RA due to their reduced muscle mass. Glomerular and tubular proteinuria are more sensitive markers of renal disease. Neiderstadt et al 13 found a very high incidence of proteinuria (55%) as a symptom of renal disease; in 75% of these there was no attributable cause and rest 25% was probably drug-induced. It was concluded that the patients without apparent cause for proteinuria which was either tubular or non-selective glomerular-tubular, was related to RA nephropathy. Microalbuminuria has also been correlated with renal damage in RA.5,14

Urinary N-acetyl glycosaminidase (NAG) serves as a marker of proximal tubular damage. Wiland et al15 studied urinary NAG levels with gold therapy. They concluded that raised levels of urinary NAG were associated with tubular damage more often than glomerular damage on entry and during treatment with gold salts. Beta-2-microglobulin is also found to be increased in serum of RA patients with proteinuria and its 24 hour urinary excretion increased in proximal tubular dysfunction.16 Cystatin C, a proteinase inhibitor produced in all nucleated cells is freely filtered in renal glomeruli and reabsorbed and catabolised in proximal tubules. It is a new parameter to assess renal function. Mangge et al17 found elevated cystatin C indicating incipient renal disease in 50% of patients with prolonged RA and advocated it as a screening test.

Plasma renin activity (PRA) has also been studied as a marker of renovascular injury in patients with RA. In a study by Mavrikakis et al18 it was found that increased PRA may occur in normotensive patients with RA with no clinical or biochemical evidence of renal involvement. This may reflect activation of the renin-angiotensin system. The positive correlation between enhanced PRA, rheumatoid factor levels and microhaematuria in RA patients may indicate inflammatory injury of the glomerular microvasculature involving the juxtaglomerular apparatus.

In this issue of JAPI Pathan and Joshi19 have done an extensive review on ‘Rheumatoid Arthritis and the Kidney’ where they have reviewed literature extensively. The important aspect of this review is the markers of renal involvement. Can these markers be made easily available and affordable? Can these techniques be reproducible and easy to use in day to day practice? If yes, then in future it will be possible to find more precise prevalence of renal involvement in RA and also the diagnosis will be made early allowing modification of treatment, if required.

REFERENCES