Renal co-morbidity in patients wih RA

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* Renal co-morbidity is common in patients with rheumatic disease based on regular assessment of serum and urine parameters of renal function.
* When patients present with both arthritis and renal abnormalities the following questions have to be addressed.

1. Is kidney disease a complication of rheumatic disease or its management, or are they both manifestations of a single systemic autoimmune disease?
2. Is rheumatic disease a complication of kidney disease and its management? (Mineral bone disorder CKD –MBD)
3. How do rheumatic disease and kidney disease affect each other even when they are unrelated?.

How to diagnose and monitor renal co-morbidity?

Renal co-morbidity may not be apparent in terms of signs and symptoms, so functional parameters must be routinely measured

1. Serum creatinine
2. Estimated GFR or Creatinine clearance
3. 24 hour urine protein
4. A/C ratio

* Table 1. Renal functions and related clinical or laboratory parameters

Function	Clinical or laboratory parameter
Excretion	Serum levels of creatinine, blood urea nitrogen, uric acid
Filtration barrier	Proteinuria as determined by dipstick test and/or by urinary protein/creatinine ratio, urinary albumin/creatinine ratio
	Hematuria as determined by dipstick test and/or microscopy
Sodium balance	Blood pressure and edema to be evaluated by clinical examination
Water balance	Serum sodium concentration, serum osmolarity
Acid–base status	Serum bicarbonate (and chloride) concentration
Renal hormones	Erythropoietin: hemoglobin level
	$1,25\text{-}(OH)_2$ vitamin D: serum calcium/phosphorus
	Concentrations, iPTH

* Renal and rheumatic manifestations of systemic autoimmune disease

* ***Rheumatoid arthritis***

Owing to their high prevalence, RA and renal disease often coincide.

Causes of renal problems in patient with RA

1. The renal toxicity of antirheumatic drugs (for example, NSAID or cyclosporine toxicity)

1. Secondary renal disease induced by the chronic inflammatory process (especially renal amyloidosis)

2. Renal manifestations of the primary disease process.

* Table 2. Renal manifestations of systemic diseases commonly seen by rheumatologists

Disease	Renal manifestation
Rheumatoid arthritis	Mesangial GN, renal amyloidosis, membranous GN
Spondylarthropathy/psoriasis arthritis	Renal amyloidosis, IgA nephropathy
Systemic lupus erythematosus	Lupus nephritis: proliferative immune complex GN, membranous GN
Sjögren's syndrome	Interstitial nephritis with renal tubular acidosis (type 1)
ANCA vasculitis	Crescentic (pauci-immune) GN, interstitial nephritis
Giant cell arteritis	Renal artery stenosis
Immune complex disease	Immune complex GN
Diffuse cutaneous systemic scleroderma	Scleroderma renal crisis, crescentic GN (with myeloperoxidase ANCA), interstitial nephritis, chronic (ischemic) kidney disease
Sarcoidosis	Nephrocalcinosis, nephrolithiasis, granulomatous interstitial nephritis
Malignancy	Nephrotic syndrome (membranous GN, minimal change disease, focal glomerulosclerosis)
Diabetes	Chronic kidney disease: diabetic nephropathy
Hypertension	Chronic kidney disease: hypertensive nephropathy

* Dosing of Antirheumatic Drugs in Renal Disease and Dialysis

TABLE 2. Pharmacokinetics and Dosing of Antirheumatic Drugs Based on Creatinine Clearance

Drug	Percent Excreted Unchanged in Urine	Plasma Protein Binding (%)	Vol of Dist L/kg	Dose for Normal Renal Function	GFR >50 (% dose)	GFR 10–50 (% dose)	GFR <10 (% dose)	Supplement-ation for Dialysis
Cyclophosph-amide	10–15	12–14	0.48–0.71	1–5 mg/kg/d	100	100	75	HD: give dose after dialysis PD: no data
Methotrexate	80–90	45–50	40–80	5–10 mg/wk	100	50	Avoid	HD: conflicting results, avoid PD: avoid
Antimalarials	50–55	55–60	150–800	Chloroquine 3.5 mg/kg/d Hydroxychloroquine 6.5 mg/kg/d	100	50	50	HD: none PD: no data
Cyclosporine	<1	96–99	3.5–7.4	Initial: 3–3.5 mg/kg/d up Max: 5.0 mg/kg/d	Avoid	Avoid	Avoid	HD: none PD: none
Azathioprine	<2	20	0.55–0.8	1.5–2.5 mg/kg q 24 h	100	75	50	HD: supplement 0.25 mg/kg PD: no data
Mycophenolate mofetil	MPAG-87	82–97	3.6	1 mg bid	100	100	100	HD: no change PD: no change
Leflunomide	43	99.3	0.13	Loading: 100 mg x 3 d then: 10–20 mg qd	No specific dosage adjustment			HD: no data PD: no data

Drug	Percent Excreted Unchanged in Urine	Plasma Protein Binding (%)	Vol of Dist L/kg	Dose for Normal Renal Function	GFR >50 (% dose)	GFR 10–50 (% dose)	GFR <10 (% dose)	Supplement-ation for Dialysis
Allopurinol	30	<5	0.5	300 mg q 24 h	75	50	25	HD: — dose PD: no data
Colchicine	20	31	4.2	Chronic: 0.5–1.0 mg q 24 h	100	50–100	25	HD: avoid PD: avoid
Sulfasalazine	10–20	99	7.5	500 mg qid	100	bid	qd	HD: no data
Sulfapyridine	negligible	50	0.4–1.2					PD: no data
5-aminosalicylic acid		43	0.26					

HD indicates hemodialysis; PD, peritoneal dialysis

Revised from Aronoff GR, Berns JS, Brier ME, et al. *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults*. 4th edition. Philadelphia, PA: American College of Physicians; 1999.

Drug	CKD stage 3 and stage 4 patients (GFR 15 to 59 ml/minute/1.73 m²)	Dialysis patients (GFR <15 ml/minute/1.73 m²)
NSAIDs	Avoid when possible or use with great caution	May be used with caution
Glucocorticoids	Short-term use possible (for example, 20 mg/day)	Short-term use possible (for example, 20 mg/day)

*Important notes

* ***Implications of unrelated chronic kidney disease in the rheumatic patient***
* Patients with impaired renal function have a substantial increase in cardiovascular risk that can be explained only in part by an increase in traditional risk factors such as hypertension and diabetes .So International guidelines stress the need for preventing and treating cardiovascular risk factors in patients with CKD, especially RA or SLE patients

* Several DMARDs cannot be used in CKD patients, due to their inherent nephrotoxicity.
* For example, NSAIDs (including cyclooxy genase-2 inhibitors) can cause acute deterioration of renal function, which is more common particularly in older patients, in CKD patients or in heart failure patients, and in states of volume depletion, because renal blood flow is dependent on renal prostaglandin synthesis.
* Glucocorticoids, acetaminophen or opioids can ***replace*** NSAIDs in CKD patients.
* Cyclosporine A is another potentially nephrotoxic DMARD. Cyclosporine causes vasoconstriction of the afferent and efferent glomerular arterioles, which leads to reductions in renal blood flow and the GFR. Cyclosporine is hence contraindicated in RA patients with renal dysfunction according to international guidelines

* Renal insufficiency also impairs the excretion of some DMARDs, which increases ***(non renal) toxicity***. For example, methotrexate is not nephrotoxic *per se* but it is excreted via the kidneys, and therefore accumulates andnis increasingly toxic along the stages of CKD .
* Some authors advocate dose reductions in CKD patients, but this can be dangerous because declines in the GFR can always happen with incident fluid loss – for example, through vomiting, diarrhea, use of diuretics or NSAIDS, sweating or fever – which further impair methotrexate clearance without a physician even being consulted. In view of the potential lethal side effects and usually available ***alternative*** treatment regimens (for example, leflunomide or biologicals), methotrexate should generally be avoided in CKD patients.
* Antimalarials, sulfasalazine, and azathioprine are only partially excreted by the kidneys, and therefore dose reductions were proposed at GFR <50 ml/minute