Renal Manifestations of Systemic Disease

Introduction
A huge variety of systemic conditions can affect the function of the kidneys, from acute illnesses (including, for example, prolonged hypotension) to drugs and more insidious illnesses. This article cannot cover all possible causes of renal disease but gives an overview of the potential renal consequences of some of the more common/more important systemic diseases. Follow links to obtain more information on the relevant disease entities, or on the specifics of management of renal disease.

Diabetic nephropathy
See separate Diabetic Nephropathy article.

Hypertensive nephropathy/nephrosclerosis
See also the separate article on Hypertension.

Renal disease can cause hypertension; however, sustained hypertension damages the vasculature of the kidneys. This is particularly so in cases of accelerated or malignant hypertension.

Early hypertensive nephropathy causes mild albuminuria and a reduced (calculated) estimated glomerular filtration rate (eGFR)\(^1\).

Hypertension causes a pathology known as nephrosclerosis, due to ischaemia affecting the glomeruli, and hyperfiltration causing intraglomerular hypertension.

Hypertension also increases the risk of chronic kidney disease through the effects of:

- Cholesterol embolisation to the kidneys.
- The presence of renal artery stenosis (particularly if bilateral).

Most patients present with significant hypertension and/or its complications (eg, cardiac failure, acute coronary syndrome, stroke) or biochemical/clinical evidence of renal impairment. There has usually been a history of hypertension for about ten years; however, some patients will present without having had any previous evidence of hypertension.

Other factors that suggest hypertensive nephropathy as the cause of renal impairment include:

- Clinical evidence of hypertensive retinopathy.
- Evidence of left ventricular hypertrophy on ECG.
- No evidence of any other cause for hypertension.
- Renal biopsy histology consistent with nephrosclerosis.
Management

- Management is through use of a range of antihypertensive agents, particularly angiotensin-converting enzyme (ACE) inhibitors/angiotensin-II receptor antagonists and diuretics; however, other agents are also used.
- Renal parameters must be monitored very closely after introduction/dose-alteration of an antihypertensive agent. Close attention to modification of other cardiovascular risk factors and renal replacement therapy are also useful in improving long-term outlook.
- Medical treatment or revascularisation (via angioplasty/stenting) may be considered for renovascular disease[2].
- However, the management of atherosclerotic renal artery stenosis in patients with hypertension or impaired renal function remains a clinical dilemma.
- The current general consensus (supported by the results of the Angioplasty and Stenting for Renal Atherosclerotic Lesions and Cardiovascular Outcomes for Renal Artery Lesions trials) argues strongly against endovascular intervention in favour of optimal medical management[3].

Vasculitides

See also separate Vasculitis article.

Primary systemic vasculitides may cause renal dysfunction through their ability to cause a focal necrotising glomerulonephritis.

Vasculitides that affect the renal vasculature tend to be those that affect medium-sized arteries. Vasculitides that tend to cause renal impairment include:

- Granulomatosis with polyangiitis (Wegener’s granulomatosis) - often presents with pulmonary haemorrhage and acute kidney injury.
- Microscopic polyangiitis (formerly known as microscopic polyarteritis nodosa - pulmonary infiltrates and rapidly progressive glomerulonephritis (RPGN) with musculoskeletal/neuropathic/CNS abnormalities).
- Churg-Strauss syndrome (allergic asthma and eosinophilia with associated renal impairment).
- Polyarteritis nodosa (predominant arteritis without significant glomerulonephritis, may manifest as glomerulosclerosis in hypertensive patients).

Systemic lupus erythematosus

- The kidneys are often affected by the systemic autoimmune process of systemic lupus erythematosus (SLE).
- This is termed lupus nephritis; there are many patterns and classifications of disease and some may resemble glomerulonephritis.
- As therapies for SLE improve, so the prevalence of life-threatening renal disease associated with the condition is falling.
- It is thought that the condition causes the formation of immune complexes that are deposited in the glomerular basement membrane, leading to activation of the complement cascade and an influx of active inflammatory cells.
- Renal impairment may be detected by routine renal function and electrolyte testing in SLE patients, or by the detection of proteinuria which can often be severe enough to cause nephrotic syndrome.
- Haematuria may be detected by urinalysis, or microscopy which may also detect glomerular casts.
- Renal biopsy is usually needed to confirm the diagnosis.
- Management is through the use of systemic immunosuppression with steroids ± cyclophosphamide, azathioprine or mycophenolate mofetil.
- Hypertension needs to be rigorously controlled, using ACE inhibitors usually if they are tolerated in terms of renal function.
- Renal replacement therapy may be needed in severe cases and transplantation may be necessary for end-stage disease, although results are poorer than for non-SLE patients.
Progressive systemic sclerosis

- Progressive systemic sclerosis (scleroderma) may affect the kidneys through the presence of a microangiopathy which may cause a chronic kidney disease, or may affect the kidneys via the precipitation of a renal crisis.
- Renal crisis tends to affect those patients with diffuse, sudden-onset dermatological involvement (the form affecting about a quarter of patients who have systemic sclerosis).
- Renal crisis affects about 10% of patients with systemic sclerosis.
- Renal crisis causes accelerated hypertension, oliguric acute kidney injury, headache, peripheral oedema and fatigue; there is a precipitate rise in urea/creatinine.
- It tends to occur within the first four years or so of diagnosis (about 75% of cases of renal crisis) but can occur at any time in the course of systemic sclerosis.
- There is a small subset of cases (~10%) that occur without the presence of hypertension.
- The condition can be ameliorated and prevented from progressing to acute kidney injury by careful monitoring for its onset and by urgent commencement of treatment with ACE inhibitors
- However, scleroderma renal crisis (characterised by malignant hypertension and oligo/anuric acute kidney injury) occurs in 5% of patients with systemic sclerosis.
- Once established, the condition must be treated with renal replacement therapy; some patients will become permanently dependent on dialysis, others may need it temporarily and remission may occur up to 18 months after starting dialysis.

Sjögren's syndrome

See also separate Sjögren's Syndrome article.

- This autoimmune sicca syndrome occurs in association with a range of other autoimmune conditions.
- Patients with primary Sjögren's syndrome often present with renal impairment, mainly from renal tubular dysfunction.
- Sjögren's syndrome can also cause renal disease as a result of glomerulonephritis or interstitial nephritis.

Myeloma

See also separate Myeloma article.

Renal impairment is a common finding in cases of multiple myeloma, affecting up to about 20% of cases at presentation and up to 50% through the course of the disease. There are several factors that predispose myeloma patients to renal impairment.

Potential precipitants of renal impairment in myeloma patients:

- Dehydration and hyperviscosity syndrome.
- Hypercalcaemia.
- Side-effects of therapy, especially non-steroidal anti-inflammatory drugs (NSAIDs) and bisphosphonates.
- Tumour lysis syndrome.
- Cast nephropathy.
- Amyloidosis.
- Light-chain deposition disease.

The presence of renal impairment can affect the patient's ability to tolerate chemotherapy; however, most patients suitable for treatment can tolerate a modified dosing regimen of melphalan and autologous stem cell transplantation. Dependence on dialysis is relatively common and some cases are treated by plasma exchange in the acute phase. If myeloma enters complete remission then patients can be considered for renal transplantation.
Cryoglobulinaemia
See separate Cryoglobulinaemia article.

- In cryoglobulinaemia, patients with cryoglobulinaemia-associated vasculitis appear to be most susceptible to renal disease, particularly if their condition is associated with hepatitis C infection[7].
- Renal pathology may be caused by thrombosis or immune complex deposition leading to membranoproliferative glomerulonephritis.
- Renal impairment tends to present as isolated proteinuria or haematuria, rather than nephrotic syndrome, nephritic syndrome or acute kidney injury.
- It usually manifests early in the course of cryoglobulinaemia (within the first five years).
- Renal disease is an indication to treat cryoglobulinaemia aggressively, as failure to do so can mean that end-stage kidney disease (ESKD) is the end result.
- Treatment is through systemic immunosuppression using corticosteroids ± azathioprine or cyclophosphamide[7].
- Plasmapheresis is used to treat acute complications related to intravascular cryoprecipitation.
- Interferon-alfa is used, particularly in hepatitis C virus-associated cases, to decrease the risk of severe complications, including renal impairment, associated with the condition.

Haemolytic uraemic syndrome
See also separate Haemolytic Uraemic Syndrome article.

- Haemolytic uraemic syndrome is predominantly a disease of children and causes a triad of microangiopathic haemolytic anaemia, thrombocytopenia and acute kidney injury.
- It is the most common cause of acute kidney injury in children and is usually precipitated by an acute infective gastroenteritis (usually Escherichia coli, Shigella spp., Salmonella spp., Yersinia spp. or Campylobacter spp.) or upper respiratory tract infection[8].
- It is treated with supportive care, dialysis as renal replacement therapy and plasma exchange in severe cases.

Sickle cell disease
See also separate Sickle Cell Disease and Sickle Cell Anaemia article.

- Many children with sickle cell disease develop hyposthenuria, an inability to form concentrated urine, that may cause nocturnal enuresis and polyuria.
- Acute severe haematuria may occur due to renal papillary necrosis or sickling within the substance of the kidney and is usually treated with DDAVP®/epsilon-aminocaproic acid.
- A post-mortem series of adult patients with sickle cell disease found that renal impairment was the cause of death in about 20% of cases[9].
- The disease causes a glomerulopathy with proteinuria and progressive renal insufficiency, leading to ESKD; renal papillary necrosis is another possible mechanism of acute renal syndromes.
- Albuminuria is a sensitive marker of glomerular damage and precedes the onset of renal impairment[10].
- There are no effective therapies to prevent the onset of chronic kidney disease other than good management of the condition in order to reduce the incidence of, and ameliorate, sickling crises.
- Great care should be taken to avoid or adjust the dose of nephrotoxic drugs which may precipitate acute or acute on chronic kidney disease.
- Those with ESKD will require renal replacement therapy and should be considered for transplantation.

Further reading & references


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