Indications for renal biopsy in chronic kidney disease

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Key Points

- **Renal biopsy carries small but definite risks**
- **The place of renal biopsy in unexplained acute renal failure and nephrotic syndrome is well established**
- **Renal biopsy may help to decide management in systemic diseases such as monoclonal immunoglobulin production and systemic lupus erythematosus**
- **In chronic renal disease with significant proteinuria, biopsy may be justified to guide decisions on immunosuppressive therapy**
- **Antihypertensive drug regimens that reduce proteinuria (typically angiotensin-converting enzyme inhibitors and angiotensin receptor blockers alone or in combination) reduce the subsequent rate of progression towards end-stage renal failure, irrespective of the histological diagnosis**
- **In suspected glomerulonephritis with haematuria but no proteinuria, there is no evidence that any form of treatment will alter the prognosis, whatever the precise histological diagnosis. Such patients must be followed long-term as a proportion develop evidence of progressive renal disease and may at that stage warrant further investigation**

KEY WORDS: biopsy, chronic kidney failure, haematuria, proteinuria

There are many clinical situations in which physicians may be uncertain whether to refer a patient to a nephrologist for renal biopsy. Biopsy is often necessary in unexplained acute renal failure (ARF) and in nephrotic syndrome (Table 1). This article addresses the more difficult question of when renal biopsy may be indicated in suspected chronic renal disease.

Renal biopsy should be performed only when the risks of the procedure are justified by a reasonable expectation that the results will have a useful impact on management. A recent comprehensive review[1] of published series gave the risks for the following procedures:

- renal biopsy: 0.06%
- surgery or embolisation to control bleeding: 0.3%
- major complications: 1.5%, and
- all complications: 7.4%.

A period of observation of at least eight hours following biopsy to allow detection of bleeding complications is considered ideal.[2] Possible indications for biopsy are listed in Table 2 and relative contraindications in Table 3.

A biopsy is occasionally justified solely for prognostic reasons: for instance, if premiums for life insurance, prospects for employment (eg in the armed services) or for emigration might be affected. Also occasionally, the risks of renal biopsy will be considered justified simply to reassure the patient or to provide a specific diagnosis or, as with suspected thin basement membrane nephropathy (TBMN), to provide a diagnosis to spare another family member (eg a child with haematuria) a renal biopsy.

In previous studies of the role of renal biopsy in influencing clinical decisions, changes in management commonly resulted from the biopsy diagnosis in patients with ARF and nephrotic syndrome, less commonly in those with

Table 1. Examples of treatment decisions that may be prompted by renal biopsy results in acute renal failure and nephrotic syndrome (this list is not exhaustive).

Acute renal failure	Pauci-immune necrotising GN	Steroids, cyclophosphamide, plasma exchange
	Proliferative GN with immune complex deposition	Treatment of underlying infection
	Interstitial nephritis	Steroids, withdrawal of causative agent
	Acute tubular necrosis	Expectant/avoidance of further insults
	Myeloma cast nephropathy	Treatment of myeloma
Nephrotic syndrome	Membranous nephropathy	Steroids, cytotoxics, cyclosporin (many UK nephrologists reserve these for the subgroup with progressive renal dysfunction or, preferably, randomise into current UK randomised trial)
	Focal segmental glomerulosclerosis	Steroids, cytotoxics, cyclosporin
	Minimal change nephropathy	Steroids; cyclophosphamide for frequent relapse; cyclosporin to maintain remission
	AL amyloidosis	Consider chemotherapy/bone marrow transplantation as for myeloma
	AA amyloidosis	Treatment of underlying cause
	Diabetic glomerulosclerosis	Glycaemic control, antiproteinuric blood pressure-lowering drugs

Table 2. Possible indications for renal biopsy.

- Microscopic haematuria
- Urologically unexplained macroscopic haematuria
- Proteinuria
- Nephrotic syndrome
- Impaired kidney function
- Hypertension

Possible renal involvement in systemic disease in:

- multiple myeloma
- monoclonal gammopathy of uncertain significance
- systemic lupus erythematosus
- antiphospholipid syndrome
- diabetes
- systemic vasculitis
- scleroderma

Possible cardiac or liver transplantation with renal impairment

- Long-term treatment with calcineurin inhibitors (cyclosporin or tacrolimus) for autoimmune conditions

Note: these abnormalities may occur in isolation or in combination (eg asymptomatic haematuria and proteinuria, haematuria with nephritic syndrome, impaired kidney function with recurrent macroscopic haematuria).

chronic renal impairment or non-nephrotic range proteinuria, and very rarely in those with isolated haematuria.[3–7] This article focuses on patients in the latter two categories in whom the differential diagnosis may be wide (Table 4).

Isolated microscopic haematuria with normal kidney function and no proteinuria

It is extremely common to find isolated microscopic haematuria with normal kidney function and without proteinuria. Up to 4% of an unselected adult population may have microscopic haematuria, and such patients are commonly referred for consideration of renal biopsy. Renal biopsy discloses glomerular disease in up to 50% of such patients, commonly indicating immunoglobulin A (IgA) nephropathy or TBMN, but there is no evidence that any form of treatment improves the (already good) prognosis in these patients.[8] One patient (out of 36) in the series of Richards *et al*[7] received cyclophosphamide and prednisolone as the result of a biopsy for haematuria. No further details were given, and it seems unlikely that haematuria was the only clue to renal vasculitis, the most likely indication for this type of treatment.

A minority of patients with isolated haematuria due to glomerulonephritis progress to develop proteinuria, hyper-

Table 3. Contraindications to renal biopsy.

Contraindication	Reason
Relative:	
Hypertension	Poorly controlled hypertension thought to increase risk of bleeding
Renal asymmetry	Suggestive of a process causing differential loss of renal mass (eg reflux nephropathy, atherosclerotic renal artery stenosis – although both these can cause proteinuria)
Decreased renal size (usually assessed as bipolar length on ultrasound)	Suggestive of chronic (therefore irreversible) renal damage, predictive of nonspecific fibrotic changes on biopsy Increased risk of complications reported in most series.
Single kidney	Accepted wisdom, based on the fact that the patient will be put into renal failure if there is irreversible damage to the kidney; however, if the patient appears likely to go into renal failure if left untreated, there is less to lose, and a biopsy may be justified if it might disclose a treatable condition
Unco-operative patient	Increased risk of complications if the patient cannot reliably stop breathing during needle puncture. Consider alternatives including biopsy under general anaesthetic, transvenous biopsy
Hydronephrosis	Obstructive nephropathy may be the cause of the renal disease (though seldom causes proteinuria) and should be investigated and treated first Increased risk of macroscopic haematuria due to biopsy needle penetrating renal pelvis or calyces
Suspected upper urinary tract infection	Urinary tract infection with white cell casts should be treated with antibiotics Active infection would contraindicate immunosuppressive treatment Biopsy might spread infection or be complicated by perinephric abscess formation
Absolute:	
Uncorrected coagulopathy	If biopsy is imperative, consider transvenous biopsy rather than percutaneous.

tension and then progressive renal failure, but these cannot be identified in advance by the biopsy appearance.[9] Several histological abnormalities, particularly the degree of tubulointerstitial fibrosis, are powerful prognostic markers, but such abnormalities are uncommon amongst patients with normal kidney function and no proteinuria. The prognosis of TBMN is sufficiently uncertain that long-term follow-up is required in progressive renal disease. It is reasonable to suggest annual urinalysis and measurement of blood pressure (BP) and serum creatinine (SCr) in primary care for such patients, reserving biopsy for those who develop proteinuria or a progressive rise in SCr.

Proteinuria without nephrotic syndrome or haematuria

Proteinuria of any degree is a potent cardiovascular risk marker, but also a risk factor for the progression of renal disease towards renal failure. The risk of progression is proportional to the amount of proteinuria, and is as accurately predicted by measurements of protein to creatinine ratio on 'spot' morning urine samples as by 24-hour urine protein estimations. Treatments that reduce proteinuria, such as angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), also reduce the risk of progression, *irrespective of the histological diagnosis*. The combination of ACEI and ARB offers additional benefit compared with either agent alone.[10] There is also additional benefit if the BP is lowered further than the conventional target of 130/80 mmHg to 120/75 mm Hg. In many of the trials of immunosuppressive therapy or fish oils in IgA nephropathy (the commonest cause of proteinuria in nondiabetics), there was suboptimal BP control.

However, in view of the additional benefit that might be gained from these therapies, most nephrologists would advise renal biopsy in patients with significant proteinuria (>1 g/24 hours or a protein creatinine ratio on a spot urine sample of > 100mg/mmol creatinine), especially if there is also haematuria. None of the informative trials has shown benefit from treatment in patients with protein excretion below these levels.[11]

Asymptomatic haematuria and proteinuria, normal kidney function

The combination of both urinary abnormalities, haematuria and proteinuria, increases the likelihood of progressive renal disease[12] compared with isolated haematuria or proteinuria and would influence many nephrologists to recommend a renal biopsy – even though the most likely diagnosis is a form of chronic glomerulonephritis for which the most appropriate treatment is antihypertensive therapy.

Table 4. Possible categories of renal disease that may be diagnosed by renal biopsy and can cause chronic renal disease, with or without proteinuria or haematuria.

Disease	Comments
IgA nephropathy	Immunosuppressives and fish oils of possible benefit
Mesangial proliferative GN without IgA deposition	Poor evidence base; most treat as for IgA nephropathy
Mesangiocapillary GN	Poor evidence base in adults; steroids + cytotoxics often tried
Focal segmental glomerulosclerosis	If primary, presents with nephrotic syndrome May be a nonspecific appearance secondary to many types of renal damage
Membranous nephropathy	More usually presents with nephrotic syndrome
Medullary cystic disease	Rare; no proven specific treatment
Glomerulocystic disease	Rare; no proven specific treatment
Diabetic nephropathy	Glycaemic control and antiproteinuric blood pressure treatment paramount
Amyloidosis	Treat underlying disorder
Infiltration by lymphoma	Renal involvement may resolve after successful chemotherapy
Cyclosporin or tacrolimus nephrotoxicity	'Striped fibrosis' classical but appearances often nonspecific
Cholesterol embolism	Complicates aortic atherosclerosis Spontaneous or following angiography
Nephrosclerosis	'Intrarenal atherosclerosis; risk factors as for atherosclerosis; nonspecific
Chronic interstitial nephritis	Consider drugs, infections
Chronic granulomatous interstitial nephritis	Treat as for sarcoidosis after exclusion of infectious and toxic causes
Hypercalcaemic nephropathy	Usually as part of milk alkali syndrome
Systemic oxalosis	Usually presents with recurrent stones May require liver transplant

GN = glomerulonephritis; IgA = immunoglobulin A.

Renal impairment with normal urinalysis or low-grade proteinuria

Renal excretory function is best assessed by estimation of glomerular filtration rate, usually with a formula incorporating creatinine level, age, sex and either body weight or racial origin. Such formulae have shown that up to 11% of the US population has some degree of renal impairment, and that the prevalence of renal impairment rises sharply with age. However, there are no data on the histological correlates of renal impairment in the general population.

'Hypertensive nephrosclerosis' is common in elderly patients with nonproteinuric renal impairment. These renal changes are closely associated with extrarenal atherosclerosis. Prevention of this type of age-related decline in renal function is likely to be best achieved by treatment of established atherosclerosis risk factors.[13]

Most nephrologists would not usually advise biopsy for renal impairment in the absence of significant proteinuria, with or without haematuria. However, this policy runs the risk of missing treatable interstitial nephritis. A recent series from North London drew attention to an apparently high prevalence of interstitial nephritis of uncertain aetiology amongst first-generation immigrant patients of Asian origin, with a possible response to steroids.[14] Further research is needed on the frequency of treatable interstitial nephritis in patients with unexplained chronic renal impairment and normal sized kidneys, and on noninvasive ways of detecting this disorder.

Atheromatous embolism

Atheromatous ('cholesterol') embolism complicating ulcerating atherosclerosis in the aorta or renal arteries, with or without precipitating factors such as aortic catheterisation, thrombolysis and anticoagulation, may also cause nonproteinuric renal disease and may indeed be part of the pathogenesis of so-called hypertensive nephrosclerosis. The characteristic histological appearance is most commonly seen in patients biopsied after an acute deterioration in kidney function, but is also common amongst patients with atherosclerosis and stable renal impairment. Partial recovery of renal function has been reported, and it is possible that cholesterol-lowering drug therapy might increase the chances of such recovery.

Suspected renal involvement in multisystem disease

Renal disease is seldom the first clinical manifestation of systemic lupus erythematosus (SLE) but is one of the most feared complications. There is little doubt that renal biopsy is imperative when deciding how to treat a patient with known SLE who presents with haematuria and proteinuria, with or without deteriorating renal function. Patients with World Health Organization class IV nephritis benefit from steroids plus cytotoxics (usually pulsed intravenous cyclophosphamide), whereas patients with less severe or more advanced, burnt-out disease may have less to gain. Advocates of an 'aggressive' biopsy policy can usually recall patients who presented solely with pyuria or isolated haematuria in whom renal biopsy disclosed type IV lupus nephritis. There are also series reported of severe lupus nephritis in patients with lupus and no urinary abnormalities. However, no such patients were included in the studies showing benefit from treatment, leaving open the question whether these patients will also gain more benefit than risk from steroids and cytotoxics.

A low threshold for renal biopsy in patients with systemic vasculitis or scleroderma is warranted as the finding of significant renal involvement is often an indication for more aggressive treatment than might otherwise be considered.

Myeloma

Renal disease in myeloma may be due to:

- cast nephropathy
- light chain deposition disease
- AL amyloidosis
- hypercalcaemia, or
- other causes such as sepsis.

Many of these conditions present as ARF. Occasionally, the diagnosis of myeloma or light chain deposition disease may be first made on renal biopsy. The yield of screening for myeloma in patients with unexplained renal impairment has not been formally studied. Such screening more commonly picks up monoclonal gammopathy of uncertain significance, unrelated to the renal disease, than full-blown myeloma.

In patients already known to have myeloma, there is no evidence that the results of renal biopsy have any useful impact on management. The presence of renal disease is an adverse prognostic marker, although mainly because renal disease is a marker for higher disease burden. Renal disease, even dialysis-dependent renal failure, does not contraindicate chemotherapy or bone marrow transplantation, and there is certainly no evidence that the type of renal disease disclosed on renal biopsy has any useful impact on the decision about how to treat the underlying disease. Many haematologists, however, tend to be more conservative when treating patients with renal involvement because of a perception that such patients tolerate chemotherapy less well.

Renal biopsy has a useful role in deciding whether to offer chemotherapy to a patient with a monoclonal gammopathy who presents with nephrotic syndrome (which may be due to amyloidosis or light chain deposition disease) when there is no conventional 'haematological' indication to offer chemotherapy. The same may be true for patients with monoclonal gammopathies of undetermined significance and unexplained chronic renal impairment, in whom renal biopsy appearances (eg cast nephropathy) might occasionally lead to a decision to institute chemotherapy.

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Clinical use of diuretics

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What are diuretics? How do they work?

Diuretics are widely used in clinical medicine, particularly in hypertensive and oedematous states. By inhibiting sodium reabsorption at different sites along the nephron, they increase natriuresis with consequent clinical benefit.[1] However, clinical goals may not always be easily achieved.

Site of action classifies the commonly used agents (Table 1).[1–3] Although most (60–70%) filtered sodium is reabsorbed in the proximal tubule, agents acting at this site (eg acetazolamide) are of relatively little clinical use in oedematous states because the increased sodium loss is offset by increased reabsorption further down the nephron in the thick ascending loop of Henle. The same principle applies to the proximal tubular effect of some thiazide diuretics.

Loop diuretics[1–3]

Loop diuretics (eg furosemide, bumetanide, torasemide) are organic anions, secreted into the tubular lumen in the proximal tubule. They act on the thick ascending loop of Henle where they exhibit high affinity for the chloride-binding site of the sodium-potassium-2 chloride (Na-K-2Cl) transporter. Binding directly inhibits sodium and chloride reabsorption. This indirectly leads to decreased reabsorption of calcium and magnesium, and interferes with urine concentrating and diluting mechanisms. Up to 20% of filtered sodium can be excreted using these agents.

Ethacrynic acid is a rarely used loop diuretic indicated in patients known to have had hypersensitivity reactions to sulphonamides and related agents.

Thiazide and related diuretics[1–3]

Diuretics of another class, the thiazides and related compounds (eg bendroflumethiazide, hydrochlorothiazide, chlorthalidone, indapamide, metolazone), are also organic anions secreted in the proximal tubule. They act in the distal tubule and connecting segment. They bind to a number of transporters, principally the sodium-chloride cotransporter (Na-Cl-CT), directly inhibiting sodium reabsorption. This indirectly increases calcium reabsorption. The maximum natriuresis is less than that achieved with loop diuretics, but combination of these classes can be especially potent.

*Potassium-sparing diuretics*1-3

The potassium-sparing diuretics include amiloride, triamterene and spironolac-

Key Points

- **Diuretics cause natriuresis in oedematous and hypertensive states**
- **Dietary salt intake restriction is essential with diuretic use**
- **Rapid adaptation by the tubule blunts the initial response to diuretic therapy**
- **Application of pharmacokinetic and pharmacodynamic principles improves the achievement of clinical objectives**
- **Sequential nephron blockade is effective in advanced chronic renal failure and heart failure**

KEY WORDS: diuretics, heart failure, kidney, nephron, oedema, pharmacodynamics, pharmacokinetics, potassium, sodium