Utility of renal biopsy in the clinical management of renal disease

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Characterizing chronic kidney disease (CKD) at all stages is an essential part of rational management and the renal biopsy plays a key role in defining the processes involved. There remain no global guidelines available to the renal community on indications for this important diagnostic, prognostic, and relatively safe test. Although most nephrologists recognize several clear indications for a renal biopsy, it is still underutilized. It not only helps the clinician to manage the patient with CKD, but it can also help clarify the epidemiology of CKD, and aid research into the pathobiology of disease with the aim of discovering new therapies. It may be useful for instance in elderly patients with CKD, those with diabetes and presumed 'hypertensive nephropathy', and in some patients with advanced CKD as part of the pretransplant work-up. In some populations (for example, immunoglobulin A nephropathy and ANCA vasculitis), renal biopsy allows disease classification that may predict CKD progression and response to therapy. For the individual, interval renal biopsy may be of use in providing ongoing therapeutic and prognostic information. Molecular advances will change the landscape of renal pathology and add a new dimension to the diagnostic precision of kidney biopsy. Organizing the multiplicity of information available in a renal biopsy to maximize benefits to the patient, as well as to the epidemiologist and researcher, is one of the challenges that face the nephrology community.

Kidney International (2014) **85,** 1039–1048; doi:10.1038/ki.2013.512; published online 8 January 2014

KEYWORDS: chronic kidney disease; clinical nephrology; kidney biopsy

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Received 23 June 2013; revised 23 September 2013; accepted 26 September 2013; published online 8 January 2014

Characterizing chronic kidney disease (CKD) at all stages is an essential part of its management. This allows the initiation of appropriate treatments with the aim of retarding CKD progression and ultimately avoiding end-stage renal disease (ESRD). Renal biopsy is often key to this process. CKD is a major health problem affecting 10–16% of the general adult population in Asia, Europe, Australia, and the United States.[1–6] Progression to ESRD remains a major clinical problem, as well as a societal and economic health burden. There are currently over a million patients worldwide on dialysis, with the number continuing to increase by ~7% annually.[7] Dialysis is very expensive, costing ~US$80,000 per patient per year in the United States.[8]

The first published report of the use of kidney biopsy in the diagnosis of medical kidney disease was in 1951.[9] Before this, although clinicians recognized clinical syndromes such as acute nephritis, nephrosis, asymptomatic hematuria, and chronic kidney failure, how these related to distinct pathologic processes remained obscure. Over the past 50 years, renal pathology has evolved gradually and, by the turn of the century, our ability to diagnose kidney disease outstripped our knowledge of pathogenesis. Renal biopsy is an essential procedure in the diagnosis of renal disease, and it is now hard to imagine that one could practice nephrology without knowing pathology. However, there remain no consensus guidelines available to the global renal community outlining the indications for this important diagnostic and prognostic test. In this review, we shall outline the current and potential future uses of renal biopsy in diagnosis, prognosis, response to treatment, and disease progression in the setting of current day nephrology.

TECHNICALITIES OF RENAL BIOPSY

An outline of the necessary elements required for an adequate renal biopsy is well described in a review by Fogo.[10] A renal biopsy should include at least 10 glomeruli,[11] although >20 may be needed to diagnose a focal glomerular disease.[12] The minimum sample size for diagnosis varies greatly depending on the underlying diagnosis. Membranous glomerulopathy, for example, may be diagnosed with a single glomerulus, whereas posttransplant diagnoses are most accurate when the cortical sample exceeds 7 glomeruli. The use of a larger

biopsy needle results in a larger fragment of tissue being collected. In one study, the use of a 16-guage (G) needle resulted in an average 70 glomeruli per biopsy, whereas the use of a 22-G needle gave 12 glomeruli per biopsy.[13] Given that each biopsy sample needs to be processed for light and electron microscopy, as well as immunofluorescence, having only 12 glomeruli is not ideal. The use of a smaller gauge needle usually requires more passes to be made,[12] and evidence suggests that >5 passes confer an increased rate of complications.[14] Furthermore, given that there is no difference in complication rates between 14-G, 16-G, and 18-G needles,[15,16] with most discomfort observed with the largest needle, it is reasonable to recommend a 16-G needle for renal biopsy in most circumstances.

LIMITATIONS OF RENAL BIOPSY

A renal biopsy provides only a cross-sectional snapshot image of the kidney. It is neither a dynamic imaging investigation nor necessarily representative of the whole kidney. As such, based on the overall clinical picture, the clinician must weigh up the relative benefits and potential toxicities of a therapy, and not just the specific pathology (see Figure 1). Further limitations are imposed that are related to the individual assessing the sample. An interesting study showed considerable international interobserver variability among an international group of renal pathologists who were asked to histologically assess features in the same slide set of renal allograft biopsies. Moreover, repeated individual feedback on individual position within the group did not reduce the variability.[17] Although some may feel that 'their' renal pathologist is better than 'the others', the findings nevertheless raise important implications for the use of renal biopsy in clinical practice and research.

SAFETY OF RENAL BIOPSY

The current standard procedure for kidney biopsy involves the use of real-time ultrasound to guide an automated spring-loaded biopsy device. Together, these two techniques have been shown to reduce complications of the procedure.[18,19] Computed tomography–guided renal biopsy is an alternative imaging tool, but it exposes the patient to the risks of radiation. There is no study that compares the rate of complications between these two imaging methods. The major complication of renal biopsy is bleeding. This includes silent hematoma (detectable on postbiopsy imaging), macroscopic hematuria, blood loss necessitating a blood transfusion, and, uncommonly, more severe bleeding requiring angiographic intervention or rarely nephrectomy.[15] Death is a rare but recognized complication.

In a recent meta-analysis, Corapi *et al.*[20] investigated the incidence and predictors of macroscopic hematuria and sufficient bleeding requiring a blood transfusion following native kidney biopsy performed using real-time ultrasound and an automated gun device. They looked at the results of 34 studies incorporating 9474 biopsies. The incidence of macrohematuria was 3.5% and requirement for transfusion was 0.9%. Blood transfusions were more likely to be needed after renal biopsy when a 14-G needle was used compared with either a 16-G or a 18-G needle (2.1% vs. 0.5%), if the systolic blood pressure was >130 mm Hg (1.4% vs. 0.1%), in patients >40 years old (1.0 vs. 0.2%), in female patients (1.9% vs. 0.6%), and in the setting of acute kidney injury

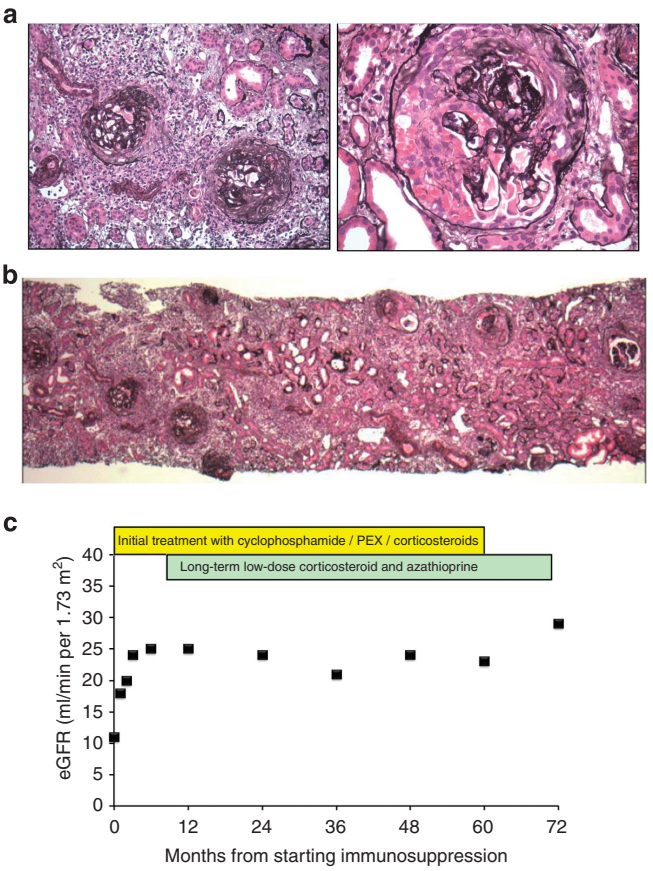

Figure 1 | A 39-year-old female bank clerk presented with a 2- to 3-month history of worsening tiredness and nocturia. Examination showed a blood pressure of 172/100 mm Hg and splinter hemorrhages in both hands. Renal function was impaired with a serum creatinine of 3.69 mg/dl and an estimated glomerular filtration rate (eGFR) of 17 ml/min per 1.73 m^2. Urinalysis revealed hematuria +++, and proteinuria was quantified at 3.3 g/day. Anti-neutrophil cytoplasmic antibodies against myeloperoxidase (MPO ANCA) titers were above the upper limit of detection (>100 IU/ml). A renal biopsy was performed. This contained 29 glomeruli, of which 17 were globally sclerosed, 10 had segmental scars, and 7 showed fibrocellular crescents of which 1 also showed intracapillary fibrin in a tuft ((**a**) hematoxylin and eosin; original magnification ×200 (left) and ×400 (right)). The globally sclerosed glomeruli displayed fibrous crescents with breaks in Bowman's capsule. Only one glomerulus appeared normal. There was severe tubular atrophy and moderate interstitial fibrosis ((**b**) hematoxylin and eosin; original magnification ×100). Immunofluorescence was negative for immunoprecipitants. Overall, these findings were in keeping with a pauci-immune chronic active segmental glomerulonephritis with low-grade disease activity. The patient was treated with a combination of plasma exchange (PEX), intravenous cyclophosphamide, and a reducing course of oral corticosteroids. She was maintained long term on a low dose of corticosteroid and azathioprine. The patient's clinical condition improved back to normal over 2–3 months. (**c**) The natural history of her renal function is shown.

Table 1 | Standard indications for renal biopsy

Hematuria of presumed renal origin (absence of infection and urological investigations normal), usually in association with other factors such as significant proteinuria, hypertension, and presence of serum biomarkers (ANCA and dsDNA)
Significant proteinuria (>1 g/day)
Unexplained renal impairment
Renal involvement of systemic disease

Abbreviations: ANCA, anti-neutrophil cytoplasmic autoantibody; dsDNA, double-stranded DNA.

(1.1% vs. 0.04%). Interestingly, in this meta-analysis, rates of macrohematuria and the need for blood transfusion were similar whether or not antiplatelet agents were withheld for ⩾7 days. Furthermore, there does appear to be a role for prebiopsy desmopressin (0.3 μg/kg given subcutaneously 1 h before biopsy) in reducing the bleeding complications after renal biopsy,[21] although at the present time this is not widely used. Overall, these data support kidney biopsy as a relatively safe procedure when carried out using current standard techniques. There is geographic variation in whether elective kidney biopsy is an inpatient or outpatient procedure; data suggest that the outpatient setting is safe with low complication rates and results in significant cost savings relative to elective inpatient biopsies.[22,23]

Pregnancy is not a contraindication to carrying out percutaneous renal biopsy. Several studies have shown that complication rates are similar to those reported in non-pregnant patients.[24,25] However, despite the safety, as there is always potential for maternal–fetal morbidity, consideration should be given to defer the procedure until the postpartum period, unless it may change management before delivery.[26,27] Furthermore, transcutaneous renal biopsy in the prone position is technically difficult in the third trimester.

RENAL BIOPSY AS A DIAGNOSTIC, EPIDEMIOLOGICAL, AND RESEARCH TOOL

A 'research' renal biopsy is one that is carried out without clinical indication and is purely for research purposes. More often, 'research' biopsies have a parallel clinical purpose, requiring an additional core to be sampled for research purposes.

If dialysis is considered an acceptable and inevitable outcome for an individual with CKD, then there are no absolute indications for a renal biopsy. This view may be one of the reasons why biopsy rates vary significantly both nationally and internationally that, in turn, will influence the reported prevalence of certain kidney diseases (for example, immunoglobulin A (IgA) nephropathy).[28–31] Nevertheless, most nephrologists recognize several clear indications for performing a renal biopsy (Table 1). However, our view is that there are good reasons to expand these indications. This will not only benefit the clinician managing CKD in the clinic, but it will better establish the epidemiology of these diseases and further research into the pathobiology and treatment. Specific examples of patient groups in whom we believe renal biopsy should more often be considered, and will not uncommonly provide unexpected information, are given below.

Renal biopsy in the elderly

CKD is increasingly common in the elderly and is more than simply the attrition of glomerular filtration rate (GFR) with age. Evidence suggests that in specific clinical settings, renal biopsy often provides crucial diagnostic and prognostic information, and changes treatment in as many as 40% of elderly patients.[32,33] Although one may anticipate the commonest renal pathology in the elderly to be chronic damage—glomerulosclerosis and tubulointerstitial fibrosis and atrophy, a likely consequence of systemic vascular disease such as hypertension or other common intrinsic renal disorders such a IgA nephropathy—a recent study showed that pauci-immune glomerulonephritis (GN) was the commonest diagnosis in very elderly patients (age ⩾80 years), occurring in 19% of those biopsied.[34] In this study, the largest of its kind, the most frequent indication for renal biopsy was acute kidney injury, accounting for almost half of the patients (46%). Progressive CKD (24%) and nephrotic syndrome (13%) were the other common indications. The investigators also determined that among very elderly patients presenting with acute kidney injury, the frequency of pauci-immune vasculitic GN affected 33% of biopsied patients, with the majority having anti-neutrophil cytoplasmic autoantibody (ANCA) seropositivity.[34] In a follow-up report, the authors showed that those who were treated with immunosuppression had a lower risk of death and ESRD than those who were not treated.[35] Selection bias must be acknowledged in these studies, as it is likely that only those elderly patients with the strongest evidence of severe disease, and who would tolerate therapy, are biopsied, whereas those not treated were likely sicker than those treated. Nevertheless, as performing renal biopsies in very elderly patients is not associated with any greater risk of complications than in younger patients,[32,36] it is a valuable diagnostic tool that should be actively considered in this group of patients given the appropriate indications and a clinical setting that maximizes the potential benefit (see Figure 2).

Renal biopsy in those with diabetes

Diabetic nephropathy, in particular that complicating type 2 diabetes, is now the leading cause of ESRD in the developed world. A commonly held opinion is that patients with diabetes who develop proteinuria in the presence of other microangiopathic complications such as retinopathy are likely to have diabetic nephropathy, and thus renal biopsy will provide little diagnostic, prognostic, or therapeutic value. However, there are now several studies that suggest that this is not the case.[37–39] Until recently, the largest of these was a study of 393 patients with type 2 diabetes for ~10 years and who underwent renal biopsy to characterize their renal disease. In all, 40% of the patients had typical diabetic glomerular disease (mean serum creatinine was 2.2 mg/dl and proteinuria 4.8 g/day), 15% had vascular changes only (mean serum creatinine was 2.7 mg/dl and proteinuria 2.8 g/day),

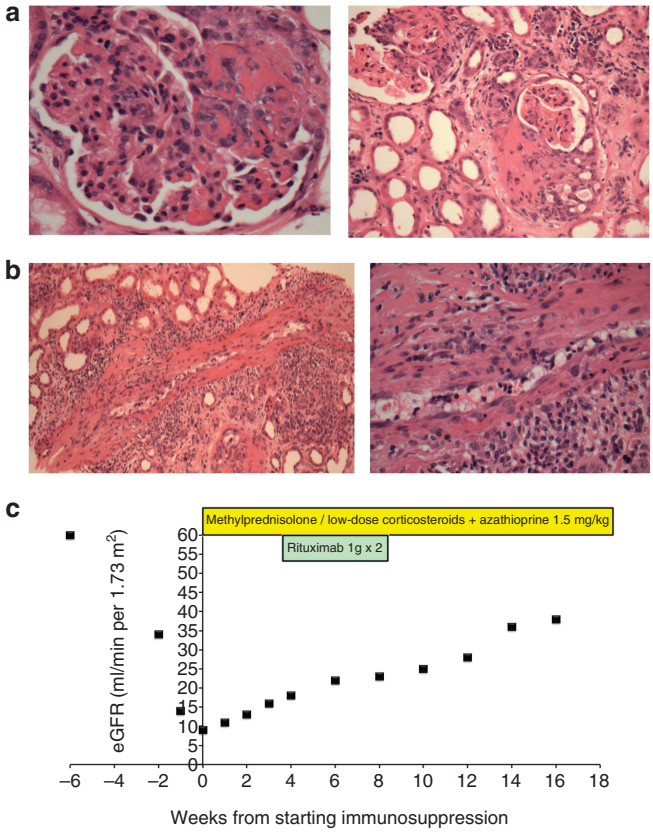

Figure 2 | A 91-year-old man presented with a decline in renal function over 2–3 months. He described feeling unwell with lethargy and joint aches for 2 years. Serum creatinine was raised at 4.85 mg/dl, with an estimated glomerular filtration rate (eGFR) of 9 ml/min per 1.73 m^2. Anti-neutrophil cytoplasmic antibodies to proteinase 3 (ANCA PR3) were above the upper limit of detection (>200 IU/ml). Other blood results revealed anemia, thrombocytosis, and elevated C-reactive protein that had persisted for over the previous 2 years. Urinalysis revealed hematuria + + +, and proteinuria was quantified at 4.3 g/day. A renal biopsy was performed. Of the 31 glomeruli sampled, 3 were globally sclerosed; at least 17 glomeruli showed segmental necrotizing lesions, some of these associated with cellular crescents; 3 glomeruli had fibrocellular crescents ((**a**) hematoxylin and eosin; original magnification ×400 (left) and ×200 (right)). An interlobular artery showed features of a segmental transmural vasculitis with fibrinoid necrosis ((**b**) hematoxylin and eosin; original magnification ×200 (left) and ×400 (right)). There was also moderate to severe tubular atrophy. Immunofluorescence was negative for immunoprecipitants. Overall, these features were in keeping with a very active pauci-immune diffuse segmental necrotizing glomerulonephritis with crescents, with evidence of extraglomerular arteritis. The patient was treated with a combination of methylprednisolone (followed by low-dose oral corticosteroids), azathioprine, and rituximab. (**c**) The natural history of his renal function is shown. In himself, the patient improved rapidly and returned to walking his dog for 5 miles a day.

and the remaining 45% had a glomerular disease other than (or in one-third additional to) diabetic nephropathy (mean serum creatinine was 2.6 mg/dl and proteinuria 5.7 g/day). The most frequent nondiabetic glomerular diseases were membranous nephropathy, IgA nephropathy, postinfectious GN, and minimal-change glomerulopathy.[39] All these conditions are potentially amenable to therapies that may improve renal outcome. The results of this study have been substantiated recently by Sharma *et al.*[40] who have published the largest study to date of renal biopsy findings in patients with both type 1 and type 2 diabetes. In this cohort of 620 patients, nondiabetic renal disease was identified in 60% of biopsies: 220 patients with nondiabetic renal disease alone and 164 patients with nondiabetic and diabetic nephropathy.

Although the studies described above and others like them are likely to represent selection bias and the effects of geographic variation, more liberal use of renal biopsy in patients with diabetes and nephropathy should be encouraged for several reasons: it would provide better epidemiological characterization of renal diseases in these patients; the availability of reliable clinicopathological correlations that are needed to avoid misleading conclusions in clinical trials; and, finally, to allow better management of individual patients and more detailed forecast of their outcome. Interestingly, a recent study in patients with type 1 diabetes and no proteinuria has shown that renal histological lesions may predict the progression to nephropathy, further supporting this view.[41] Select groups of patients with diabetes in whom renal biopsy may be indicated are outlined in Table 2.

Table 2 | Suggested indications for renal biopsy in patients with diabetes with the appropriate clinical setting

Nephrotic-range proteinuria, but an absence of other diabetic microangiopathic complications (especially in type 1 diabetes[97])
Diabetes for an insufficient length of time for nephropathy to develop[40] (usually 10 years; this may include those with subnephrotic-range proteinuria and/or those with unexplained renal impairment)
Patients with minimal comorbidity in whom immunosuppressive treatment for an alternative diagnosis may be considered
Patients in whom a transplant may be considered and the natural history of their renal disease has been unusual for diabetic nephropathy

Microscopic hematuria of presumed renal origin *in isolation* is an insufficient indication for renal biopsy in patients with diabetes, and should be managed as in other patients—with renal biopsy indicated when it is associated with significant proteinuria or in the presence of other markers of disease, for example, seropositivity for anti-neutrophil cytoplasmic autoantibodies (ANCAs) or antibodies to double-stranded DNA (dsDNA).

Renal biopsy in those with 'hypertensive nephropathy'

African Americans are more likely to develop progressive CKD than European Americans, and this is true for all the leading causes of ESRD.[42] In particular, for hypertension-associated CKD, there is a threefold increase in the incidence of ESRD for African Americans overall, which is magnified at younger ages. There is a genetic contribution to this excess risk with a region of chromosome 22 that encodes the *apolipoprotein L1* (*APOL1*) gene, being associated with hypertensive ESRD in this population.[43] *APOL1* gene variants have also been associated with focal and segmental glomerulosclerosis (FSGS). An interesting case–control substudy of the African American Study of Kidney Disease and Hypertension (AASK) aimed to further understand the role of *APOL1* gene variants in clinically diagnosed hypertensive

nephropathy in this population. Compared with African-American controls with normal kidney function and some with mild or moderate hypertension, the authors found that in all of the 675 AASK cases studied, *APOL1* gene variants strongly associated with renal disease attributed to hypertension, and that this association was strongest in those with more severe proteinuria and more rapid GFR decline despite equivalent blood pressure control.[44] Taken together with a previous histopathological substudy that showed that lesions of focal and global glomerulosclerosis were commonly present in the AASK cohort,[45] an argument may be made as to a potential role for increasing the frequency of renal biopsy in the population of these patients who have variants of the *APOL1* gene in helping to define further why progression of CKD continues in this population despite good blood pressure control.

Renal biopsy in those with advanced CKD

In 2010, 16,843 renal transplants were carried out in the United States, and an additional 70,807 patients were on the transplant waiting list.[8] For patients with advanced CKD or ESRD, receiving a renal transplant is their best therapeutic option. Many patients with ESRD receive a kidney transplant without knowledge of their original disease. This can be an important knowledge gap, as many glomerular diseases recur after transplant. The most often recurring diseases are primary FSGS, membranoproliferative GN (MPGN), membranous nephropathy, and atypical hemolytic uremic syndrome (see review in Ponticelli and Glassock[46]). Clearly, predicting the likelihood of recurrence requires prior knowledge of the diagnosis. Such prior awareness of a potentially recurrent condition can affect management before and after transplant. One example is atypical hemolytic uremic syndrome, for which the risk of posttransplant thrombotic microangiopathy and graft loss is high. Here, pretransplant counseling discussion is important, as well as consideration of prophylactic plasma exchange and potential availability of the complement inhibitor eculizumab.[47] Although genetic testing may help toward making the diagnosis, there are as yet many uncharacterized inherited complement abnormalities that may or may not inform the patient and physician about recurrence. In this scenario, carrying out a renal biopsy that includes all elements (light and electron microscopy as well as immunofluorescence) can reveal a significant diagnosis occasionally even in advanced CKD. Thus, we would suggest consideration of the benefits of renal biopsy in patients with advanced CKD who are suitable for renal transplantation, and in whom there is diagnostic uncertainty about the cause for their CKD. However, the relative risks of carrying out a kidney biopsy in advanced CKD should be appreciated. Bleeding complications may be increased for two reasons. First, because of CKD itself,[20] and second because of the smaller cortical thickness that potentially confers a greater chance of hitting the renal vessels within the pedicle.

RENAL BIOPSY AS AN ADJUNCT TO DIAGNOSIS: 'DIAGNOSTIC CROSS TALK'

There are currently no noninvasive investigations that are sufficiently sensitive and specific to provide accurate diagnoses in most types of renal disease. There are a number of scenarios where renal biopsy can be used as an adjunct to clarify/support/confirm a diagnosis suggested by the results of other tests. For example, in a patient presenting with urinary abnormalities such as hematuria and/or proteinuria and who is also seropositive for the antibodies against double-stranded DNA or extractable nuclear antigens, the renal biopsy will help confirm the histological characteristics compatible with the diagnosis of lupus nephritis or an interstitial nephritis typical of Sjögren's syndrome. Thus, there is 'diagnostic cross talk' between the results of the renal biopsy and those of other investigations.

Diagnostic cross talk is particularly important in the setting of renal transplantation, with antibody-mediated rejection (AMR) being a good example. Graft rejection represents one of the major causes of graft dysfunction in the first few months after a kidney transplant. This topic has been covered recently in a review by Nankivell and Alexander[48] where Nankivell comments that 'although an increase in serum creatinine points to rejection, subclinical rejection may be apparent only on biopsy of the organ and, in the absence of renal dysfunction, can damage the allograft. The histologic findings on biopsy influence the prognosis and the choice of therapy.' These comments support a role for protocol allograft biopsies, and this topic has been covered elsewhere and will not be discussed further here.[49]

Early posttransplant AMR is usually caused by preformed donor-specific antibodies (DSAs) to antigens expressed on the graft microvasculature. Tissue injury is mediated through these antibodies activating the complement. AMR is diagnosed on the basis of characteristic histological injury (acute tubular injury, neutrophils in peritubular capillaries, or fibrinoid necrosis of arteries), evidence of circulating DSAs, and interaction of these DSAs with the graft (sometimes triggering detectable C4d deposition in the peritubular capillaries). C4d is detected by immunofluorescence microscopy or immunohistochemistry, with the former being the most sensitive.[50] The increasing sensitivity to detect human leukocyte antigen–DSAs with solid-phase serologic assays has accordingly reduced the threshold for allograft biopsy to diagnose AMR. Furthermore, this is often in the face of stable and/or excellent allograft function (based on serum creatinine). The mere presence of DSA does not mean that AMR is inevitable, and conversely AMR may occasionally be suspected histologically without detectable human leukocyte antigen–DSA. The latter in ABO-incompatible transplants is usually due to the presence of DSA against non-human leukocyte antigens.[51]

Although AMR shows the relevance of circulating biomarkers in urging the clinician to perform a renal biopsy, the converse is also true, with histological findings prompting the search for pathogenic and prognostic factors. The past few years have seen advances in unraveling the pathophysiology of

primary FSGS. There may be a pivotal role for the circulating levels of a permeability factor, the most recent candidate being the soluble urokinase plasminogen activator receptor. A high concentration of soluble urokinase plasminogen activator receptor has been observed in two-thirds of patients with FSGS, and high levels have been shown to predict recurrence after transplantation.[52] These observations raise the possibility of treatments for FSGS, such as those that may remove the circulating factors (for example, plasma exchange).

As a final example of diagnostic cross talk, MPGN has traditionally been classified into types I, II, and III based on the localization and ultrastructural appearance of immune deposits rather than the composition of these deposits. It is now understood that subsets of MPGN types I and III that contain C3 alone (in the absence of immunoglobulin) are mediated by inherited or acquired mutations in the alternative complement pathway. These subsets of MPGN I and III are now referred to as 'C3 glomerulonephritis,' and together with type II MPGN they are known as 'C3 glomerulopathies.'[53] A diagnosis of C3 glomerulopathy prompts the clinician to pursue a specific diagnostic and treatment algorithm including investigations looking for genetic defects, autoantibodies to complement factor H, and genetic deficiencies in other complement proteins.

PREDICTING DISEASE PROGRESSION AND RESPONSE TO THERAPY FOR THE POPULATION

Over the past few years, renal biopsy has been used on a population scale to devise histological classifications for specific diseases. Examples that we will discuss here are IgA nephropathy and ANCA-associated vasculitis, but others include lupus nephritis and FSGS. The rationale for these classifications is that they may predict disease progression and, more importantly, response to therapy.

IgA nephropathy

The Oxford Classification of IgA nephropathy provides an internationally recognized and reproducible histopathological classification for this disease. It was based on the analysis of 265 renal biopsy sections from around the world and involved a two-part process. First, reproducible histological features of IgA nephropathy were characterized,[54] and, second, these were distinguished on their ability to predict disease progression independent of the clinical parameters.[55] Six variables were identified initially as reproducible—mesangial cell hypercellularity, segmental sclerosis, endocapillary hypercellularity, cellular or fibrocellular extracapillary lesions, interstitial fibrosis or tubular atrophy, and arterial lesions. The median follow-up period in the second part of the study was 69 months, during which time 22% of the patients (58 patients) progressed with a 50% decline in renal function and 13% reached ESRD. Of the initial six histological variables identified, four were shown to relate independently of clinical parameters to disease progression. These were mesangial hypercellularity, segmental glomerulosclerosis, endocapillary hypercellularity, and interstitial fibrosis or tubular atrophy. The authors recommended that these variables be clearly reported in biopsy reports as histological predictors of IgA nephropathy.

The Oxford Classification may have incidentally identified histological predictors of response to treatment. Of all the pathological variables considered, only endocapillary proliferation appeared to relate to response to immunosuppressive therapy in this retrospective study. In patients who received no immunosuppression, the rate of GFR decline was -5.4 ± 11.1 ml/min per $1.73\,m^2$ per year in those with endocapillary lesions and -2.6 ± 5.1 ml/min per $1.73\,m^2$ per year in those without these lesions ($P = 0.02$). This difference disappeared in those treated with immunosuppression, suggesting indirectly that those patients with endocapillary lesions may respond to immunosuppression. This finding is supported by other studies.[56]

Although a major step forward in the classification of IgA nephropathy and a role model for other glomerular diseases, the Oxford study had some limitations. The data collected were retrospective but the findings provide strict criteria on which future prospective trials of therapies may be based. It also excluded those patients with mild disease (proteinuria $<0/5$ g/day), those with advanced disease (GFR <30 ml/min per $1.73\,m^2$), and those with rapidly progressive IgA nephropathy, and thus the significance of crescents and necrosis was not evaluated (although these were present in insufficient numbers in the original study). However, these issues have since been addressed by others who have not only confirmed the value of the Oxford classification but added to its power.[57–59]

ANCA-associated vasculitis

ANCA-associated vasculitis is uncommon (incidence $\sim$20/million of population), with a mortality rate of 25% at 5 years.[60] ANCA vasculitis frequently affects the kidneys, and renal involvement is an important predictor of both morbidity and mortality,[61] with renal biopsy being the gold-standard investigation for both diagnosis and prognosis.[62,63] A recent study by Berden *et al.*[64] evaluated the predictive value of renal histology in ANCA-associated GN. Here, glomerular disease was classified as focal ($\geqslant$50% normal glomeruli), crescentic ($\geqslant$50% glomeruli with cellular crescents), mixed ($<$50% normal, $<$50% crescentic, and $<$50% globally sclerotic glomeruli), and sclerotic ($\geqslant$50% globally sclerotic glomeruli). The authors showed that this classification was a predictor for estimated GFR at 1 and 5 years independent of age, disease therapy, and renal function at baseline. Whereas the focal and crescentic classes showed good chances of renal recovery and response to therapy, respectively, the mixed class had an intermediate risk of disease progression to ESRD and the sclerotic class a high risk of developing ESRD. Although this was considered a well-conducted and useful study, it does have some limitations. There was no assessment of interobserver variability for assessment of histology into the four categories of disease, and the study was conducted entirely in Europe, and thus it needs to be validated in other geographical and ethnic cohorts.

In a nested histological subanalysis of the RITUXVAS study—which compared the B cell–depleting therapy rituximab with the standard of care, cyclophosphamide, in patients with ANCA vasculitis—T-cell tubulitis was an independent predictor of estimated GFR at 1 year and tubular atrophy an independent predictor at both 1 and 2 years.[65] Finally, recent histopathological studies suggest a role for the alternative complement pathway in the pathogenesis of ANCA vasculitis.[66,67] Taken together, these findings suggest possible roles for targeting the activated T-cell and complement pathway as alternative therapeutic targets in ANCA disease and show the utility of renal biopsy as a research tool that may guide future research into therapies for such diseases.

ASSESSMENT OF DISEASE PROGRESSION AND RESPONSE TO THERAPY FOR THE INDIVIDUAL: INTERVAL RENAL BIOPSY

Repeating the renal biopsy in individual patients is not practiced widely. Although disease classifications are useful at a population level, it is harder to demonstrate that they are of value in providing clinically meaningful prognostic information for the individual. Given that serum creatinine is a poor marker of renal function,[68] this is best provided by interval biopsy both to assess disease progression and response to therapy. This is most practiced in lupus nephritis and in renal transplantation, although it is assuming a wider role in other diseases such as ANCA vasculitis.

Interval biopsy in lupus nephritis

Although systemic lupus erythematosus may involve any compartment of the kidney, glomerular involvement is the best studied and correlates well with presentation, course, and treatment of the disease.[69] Current treatments for lupus GN—and studies of newer therapies—are guided by the International Society of Nephrology/Renal Pathology Society (ISN/RPS) histological disease class,[70] with appropriate consideration given to clinical parameters and degree of renal impairment. Remission of lupus nephritis (glomerular, tubulointertstitial, and vascular disease)—histologically associated with the absence of activity—is thought to clinically correlate with the absence of hematuria and resolution of proteinuria. However, current criteria defining remission on proteinuria may underestimate those achieving a meaningful histological remission.[71,72]

Experts have argued that patients with lupus nephritis should have an interval renal biopsy to define the presence of ongoing disease and the extent of background injury.[73] Rebiopsy would not only identify those patients who have not responded and need extra treatment, but would also avoid overtreating histological responders and/or those that have irreversible and extensive injury. Defining the extent of chronic damage is also important, as 50% of these patients will experience disease relapses, and future decisions about the type and dose of immunosuppression may be balanced by the overall degree of histological recovery that may be achieved. In addition to defining disease activity following treatment, repeat biopsy should be considered at the time of renal disease relapse, as patients can switch ISN/RPS class and this may alter management.[74,75] A similar approach could also be considered for other GNs including ANCA-associated vasculitis, IgA nephropathy, and membranous nephropathy.

Interval biopsy in renal transplantation

A role has been suggested for preimplantation biopsy as a means of judging the quality of a donor kidney (deceased and live) in addition to the usual variables (for example, age, body size, and immunological mismatch). Although a number of histological scoring systems exist, such as the Maryland aggregate pathology index,[76] their reproducibility and application to clinical decision making remain to be defined. In addition, given the focal nature of renal biopsy, these histological findings are unlikely to lead to organs being discarded, except where there is the most florid disease. Preimplantation biopsies do, however, provide a useful baseline to which future pathology may be compared.

In the posttransplant period, most renal allograft biopsies are taken to assess the cause for graft dysfunction, with the timing of the biopsy influencing the differential diagnosis.[77] Renal allograft biopsy remains the gold standard by which diagnostic and prognostic information is obtained after transplantation. Furthermore, the results of these biopsies have been shown to change the diagnosis and treatment plan (made solely on the basis of clinical and laboratory findings) in ~40% of patients and lead to a reduction in immunosuppression in ~20% of patients.[78] This benefit was independent of the time since transplantation and extended to biopsies obtained after the first transplant year.[78] Given that immune-mediated and inflammatory processes, such as AMR and BK virus nephropathy, may progress rapidly within the allograft, and lead to irreversible fibrosis and atrophy, comparing the histological changes serially is important if one is to decide on the relative gains and potential consequences of augmenting (or reducing) therapy.

RECENT ADVANCES: PATHOLOGY AT THE MOLECULAR LEVEL

In recent years, molecular biology research has moved on from studying single genes, their transcripts (messenger RNA (mRNA)), or proteins to studying groups of molecules within a given domain in parallel with microarray technology.[79] In addition, there has been a growing interest in the role of microRNAs in kidney homeostasis and disease.[80] MicroRNAs are endogenous, short noncoding lengths of RNA that control the expression of many genes. The microRNAs may be detected by a number of techniques including microarray technology and quantitative PCR. The hope is that such 'omics' approaches will serve as a molecular microscope focused on new ways of examining renal biopsy tissue and help elucidate disease mechanisms and identify novel biomarkers that will aid diagnosis, prognosis, and treatment.[81,82] Microarray techniques have the advantage over conventional pathology in their capacity to identify and quantify thousands of transcripts at once and in their ability

to measure early and rapid changes in disease processes before the resulting pathological lesions are detectable. However, microarrays cannot give information on anatomical relationships and the source of a particular transcript. Nevertheless, it is likely that these molecular markers together with histology will add to the diagnostic precision of the kidney biopsy. This is a prerequisite if new noninvasive biomarkers—such as urine proteomics—are to be validated against the biopsy as a gold standard alongside the clinical scenario.[83] Despite the advances that have been made over the past few years within the field of molecular characterization of the renal biopsy, there have been few clinically relevant correlates.

Renal transplantation

Within nephrology, the largest experience of these new molecular technologies has been within the field of transplantation. An example of how the addition of molecular information has improved diagnostic precision is the initial studies recognizing the value to AMR diagnosis of detecting the complement component C4d in peritubular capillaries, with the subsequent recognition and definition of C4d-negative cases that have significantly expanded the spectrum of AMR diagnosis. This has revolutionized our ability to diagnose AMR. There have also been repeated observations that groups of genes change their expression in a coordinated manner, reflecting major biological processes such as inflammation or repair.[82] A limitation is that these molecular phenotypes are not necessarily disease specific, with many different disease processes in transplanted kidneys having a similar molecular signature. Furthermore, translation of these molecular studies to the clinic will require these tests to be validated across multiple laboratories, their interpretation standardized, and their methodology simplified. However, as these issues are resolved, the era of personalized medicine microarray analysis will augment significantly our current diagnostic work-up of an individual patient.

Disease pathophysiology

Idiopathic membranous nephropathy (IMN) has been recently pathogenically associated with antibodies to the phospholipase A2 receptor (PLA2R)[84] versus their absence in secondary disease.[85] The target antigen can be detected in the glomerular deposits, and this associates strongly with detection of antibodies to PLA2R in the blood.[86] As greater evidence accumulates for the treatment of IMN,[87,88] studies are needed to correlate glomerular PLA2R staining and blood PLA2R antibody titers with disease progression and response to treatment. The B cell–depleting monoclonal antibody, rituximab, has emerged as a promising therapy for IMN.[89] The limited data that exist suggest that rituximab depletes circulating PLA2R before a reduction in proteinuria is seen.[87] This suggests that the blood PLA2R level may indeed reflect immunological activity rather than the phenotypic injury associated with changes in proteinuria in IMN. How rituximab temporally affects glomerular PLA2R staining is unclear. Although a patient in the clinic who presents with nephrotic syndrome and is also positive for the PLA2R antibody may be considered to have IMN, a renal biopsy will allow assessment of chronic renal damage and other associated pathologies. Together, these data will allow the clinician to make an informed decision of the relative benefits of immunosuppressive therapy. Serial renal biopsy would be helpful in this setting and would help clarify the pathobiology and natural history of native IMN. In a recent small study, recurrence of membranous nephropathy following transplantation was associated with positive glomerular PLA2R staining in 10 of 12 cases, whereas PLA2R staining was present in only 1 of 8 cases of *de novo* membranous disease.[90] These findings support data from an earlier study.[91]

Disease diagnosis and classification

Along with the identification of soluble urokinase plasminogen activator receptor, the enquiry into the molecular pathogenesis of FSGS has become more feasible with techniques such as laser capture microdissection (LCM) that allow the investigation of the glomerular gene expression profiles of patients with primary FSGS using a microarray of mRNA isolated from formalin-fixed renal biopsies.[92] LCM and mass spectrometry has also shown itself to be a valuable proteomic tool, allowing the characterization of rarer forms of renal amyloidosis from renal biopsy.[93] These include those associated with deposition of fibrinogen α-chain, apolipoprotein A-1 and A-IV, transthyretin, and gelsolin. Such precise phenotyping should allow better genetic counseling and disease-specific treatments to be implemented. LCM and mass spectrometry is also useful in determining the type of immunoglobulins and complement factors in immune complex and complement-mediated glomerulonephritis, respectively.[94] Finally, newer stains for IgG subtypes have allowed the identification of novel monoclonal forms of proliferative GN[95] and IgG4-associated autoimmune interstitial nephritis.[96]

CONCLUSIONS

A renal biopsy is a relatively safe procedure with a well-defined risk profile enabling patients to make shared decisions about the merits of having one. It forms an invaluable part of the diagnostic process and also provides prognostic and mechanistic insights. It is a rich source of information and it is likely that it will deliver specific molecular and cellular patterns of disease that will enable targeted therapy in the future. Renal biopsies also facilitate 'bedside to bench' research that further defines the mechanisms and pathogenesis of progressive renal injury, with the potential of new therapies.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

ND is supported by a British Heart Foundation Intermediate Clinical Research Fellowship (FS/13/30/29994).

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