PAST AND PRESENT OF RENAL BIOPSY IN THE MANAGEMENT OF PATIENTS WITH GLOMERULAR DISEASES

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Abstract

Chronic kidney disease (CKD) is a major health problem affecting 10–16% of the general adult population in Asia, Europe, Australia, and the United States^(1,2,3,4,5,6). Progression to end stage renal disease (ESRD) remains a major clinical problem because the number and the cost: there are currently over a million patients worldwide on dialysis, with the number continuing to increase by ~7% annually⁽⁷⁾ and the cost of dialysis is very expensive, costing ~US\$80,000 per patient per year in the United States⁽⁸⁾.

Since 1951 when was the first published report of the use of kidney biopsy in the diagnosis of medical kidney disease⁽⁹⁾, 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.

Keywords: renal biopsy, glomerular diseases, chronic kidney disease, hematuria, proteinuria.

Rezumat

Boala renală cronică este o problemă majoră de sănătate care afectează 10-16% din populația adultă din Asia, Europa, Australia și Statele Unite^(1,2,3,4,5,6). Progresia spre boala renală în stadiu terminal rămâne o problemă clinică majoră, din cauza frecvenței și costurilor pe care le implică: la nivel mondial, există în prezent peste un milion de pacienți în dializă, numărul acestora continuând să crească cu ~7% anual⁽⁷⁾, iar costul dializei este foarte ridicat, atingând ~ 80.000 USD pe pacient pe an în Statele Unite⁽⁸⁾.

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Începând cu 1951, când a fost publicat primul raport privind utilizarea biopsiei renale în diagnosticul afecțiunilor renale⁽⁹⁾, biopsia renală este o procedură esențială și în prezent a devenit greu de imaginat că se poate practica nefrologia fără a cunoaște diagnosticul histopatologic. Cu toate acestea, nu dispunem de ghiduri consensuale care să precizeze indicațiile pentru acest test diagnostic și prognostic important. În lucrarea de față, vom prezenta utilitatea actuală și perspectivele viitoare ale biopsiei renale în ceea ce privește diagnosticul, prognosticul, evaluarea răspunsului la tratament și a evoluției afecțiunilor din sfera nefrologiei.

Cuvinte cheie: biopsie renală, boli glomerulare, boli renale cronice, hematurie, proteinurie.

Background

The introduction of percutaneous renal biopsy in clinical practice has led an important step to a new era of pathology and pathogenesis of glomerular diseases. The diagnosis of glomerular disease in renal biopsy specimens often has at least 5 steps that may occur in different sequences:

- 1) preliminary review of available clinical data prior to specimen examination,
- 2) light microscopic examination,
- 3) immunohistologic examination,
- 4) electron microscopic examination, and
- 5) integration of all pathologic and clinical data into a final interpretation and diagnosis.

What are the major clinical uses for a renal biopsy?

Ideally, the informations derived from a renal biopsy must need the clinician to diagnose kidney disease; to assess prognosis; to monitor disease progression; to aid in the selection of a rational approach to therapy; to monitor and assess response to treatment⁽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 post transplant 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-gauge (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, 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.

Several large prospective and retrospective studies provide an estimate of the frequency of complications after percutaneous renal biopsy^(17, 18, 19, 20, 21, 22, 23, 24): (1) death: < 0.1%; (2) major bleeding requiring nephrectomy or surgical hemostasis: 0.1% to 0.5%; (3) arteriovenous fistula requiring invasive intervention: 0.1% to 0.5%; (4) blood transfusion requirement: 0.3% to 7.4%; (5) uncomplicated hematoma: 10 to 90%; and (6) transient macroscopic hematuria: 1% to 10%. An important step before renal biopsy is to search for factors increasing the risk of complications, particularly bleeding. Although there are no definitive ways to predict which patients will experience complications, several predisposing factors to bleeding have been identified, at times inconsistently.

High blood pressure, age, a decreased GFR,

obesity, anemia, low platelet count and small center size (< 30 biopsies/year) are associated with an increased risk of bleeding^(20, 24, 25, 26, 27, 28). Amyloidosis was reported to be associated with bleeding⁽²⁵⁾, although such association was not found in large study by Tøndel *et al*⁽²⁴⁾. As discussed below, hemostasis disorders, anticoagulant or antiplatelet therapy, and certain anatomic conditions, may also contraindicate or complicate percutaneous renal biopsy.

A recent systematic review and meta-analysis of hemorrhagic complications after percutaneous native kidney biopsy using ultrasound guidance and automated spring-loaded biopsy device reviewed 34 publications and concluded that the predictors of erythrocyte transfusion were: the needle gauge (14 vs. 16 or 18), sex (female), serum creatinine (≥ 2 mg/dL), low hemoglobin prior biopsy (≤ 12 g/dL) and acute kidney injury⁽²⁷⁾.

Well-trained nephrologists can perform renal biopsy as well as radiologists^(29, 30). Automated biopsy guns have superseded Tru-cut needles and are probably used in most centers⁽³¹⁾. Several studies suggested that 14-18G needles are appropriate for percutaneous renal biopsy^(18, 32). The use of an automated biopsy gun in combination with real-time ultrasound guidance was reported to provide adequate samples in nearly 99% of cases, with severe hemorrhagic complications occurring in less than 0.1%. This method can be considered the gold standard^(18, 25). The use of bedside ultrasound to assess the location and depth of the kidneys was reported as a reliable alternative to real-time guidance⁽³⁰⁾. In some instances, especially in obese patients, it may be necessary to perform renal biopsy under guidance by CT-scan instead of ultrasound. Transjugular renal biopsy has been reported

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to be a safe and reliable alternative to conventional percutaneous renal biopsy in patients with obesity⁽³³⁾ or those at risk for bleeding, including high-risk patients with coagulopathy and thrombocytopenia^(34, 35). In these studies, transjugular renal biopsy provided diagnostic yield and safety similar to those of percutaneous approach. However, in most countries, the use of transjugular renal biopsy is limited to a few centers because of the necessity of skilled interventional radiologists.

Laparoscopic renal biopsy has also been reported as an alternative for patients in whom percutaneous approach was not feasible or was contraindicated, because of obesity, solitary kidney, anticoagulation or coagulopathy, or failed percutaneous biopsy. However the number of patients included in these studies was limited and no study has compared the safety of percutaneous, transjugular and laparoscopic renal biopsy in patients at high risk for bleeding. In addition, when considering these procedures, one should carefully contemplate the risk of general anesthesia, perioperative risk and recovery time.

In which clinical settings is a renal biopsy most useful as an aid in the evaluation and management of a patient with undiagnosed kidney disease?

Acute kidney injury (AKI). In the absence of an explanation for AKI when the patient is evaluated initially or when recovery of renal function has not occurred after 3 to 4 weeks of supportive therapy that may include acute dialysis, a kidney biopsy is recommended to distinguish between acute tubular necrosis and those diseases that may require a different therapeutic approach.

Chronic kidney disease (CKD). A renal biopsy may be useful in patients with unexplained CRF and normal-sized kidneys. In contrast, a biopsy is not recommended in the presence of undersized kidneys that have severe parenchymal damage including glomerulosclerosis, chronic vascular injury, and interstitial fibrosis. Kidneys with this degree of disease have a greater propensity for biopsy-induced bleeding.

Nephrotic syndrome. A renal biopsy is generally indicated in infants younger than 1 year of age (possible congenital nephrotic syndrome) and in adults with the nephrotic syndrome and no evidence of systemic disease before therapy is initiated. Children with the nephrotic syndrome are likely to have steroid-responsive disease; thus, biopsy is reserved for those who are unresponsive to a short course of steroids.

Proteinuria. In the presence of persistent proteinuria of 2 g/24 hours/1.73 m² or more and especially when associated with an abnormal urine sediment or documented

functional deterioration, a renal biopsy may be useful to detect an underlying kidney disease. Isolated orthostatic proteinuria is not an indication for biopsy.

Hematuria. Renal biopsy should be reserved for those individuals with microscopic hematuria that has persisted beyond 6 months; in patients with episodic gross hematuria; or in individuals with a family history of hematuria, particularly when associated with proteinuria and/or abnormal urine sediment. Diagnostic possibilities include immunoglobulin A nephropathy, benign essential hematuria, thin basement membrane disease, and Alport syndrome. Renal biopsy is rarely helpful in the clinical setting of short-term, isolated microscopic hematuria. Secondary causes of hematuria such as those resulting from abnormalities in the lower urinary tract must be excluded.

Systemic disease. Disorders such as systemic lupus erythematosus, diabetes mellitus, Schönlein-Henoch purpura, Goodpasture's syndrome, polyarteritis nodosa, various dysproteinemias, and Wegener granulomatosis often manifest kidney involvement. Renal biopsy is frequently useful to establish or confirm a diagnosis and guide subsequent treatment.

Transplant allograft. Renal biopsy is used extensively to differentiate between the various forms of rejection and other causes of kidney failure such as acute tubular necrosis. All these indications are not absolute. In each situation, if associated clinical and laboratory investigation suggest a predictable histological pattern, renal biopsy may not be required. So, the contraindications of kidney biopsy are:

1. **absolute:** small kidneys; abnormal coagulopathy; uncontrolled hypertension

2. **relative:** solitary kidney; uncooperative patient; unable to lie flat on bed.

Is a single histological diagnostic enough?

Ideally, the renal biopsy should identify a specific diagnosis and the severity of the renal disease, can be valuable in improving prognostic accuracy and provide the basis for a decision about specific therapy. Unfortunately, the pathologic diagnosis is often not specific and definitive one; as a result the prognosis and response to therapy cannot always be predicted with confidence⁽³⁶⁾. Prognostic indicators can be derived from a variety of lesions of renal biopsy: lesions such as glomerulosclerosis, arteriosclerosis, and interstitial fibrosis, if severe and diffuse, indicate a poor prognosis because they are irreversible, slowly progressive, and not responsive to treatment.

(Table 1) On the other hand, intracapillary proliferative and exudative glomerular hypercellularity, even when pronounced, is often completely reversible and does not necessarily indicate a poor prognosis.

(Table 2) Glomerular inflammatory process when associated with necrosis and destruction of basement membranes are more likely to result in glomerular sclerosis. Large crescents (more than 50% of the glomerular circumference) will instead become fibrotic and destroy the glomerular tuft.

(Table 3) Glomerular capillary thrombi may resolve without residual damage, even without anticoagulant therapy^(37, 38, 39). In the arteries intimal edema and hyaline insudation seem to be potentially reversible, in contrast with an arteritic inflammatory process associated with necrosis who leads

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to segmental scarring and destruction of the elastic lamina⁽³⁸⁾. In general, the presence of severe interstitial fibrosis, tubular atrophy and diffuse glomerular sclerosis indicates irreversible lesions and should discourage an aggressive treatment. Lesions such as increased cellularity, fibrinoid necrosis and cellular crescents are potentially reversible and warrant aggressive treatment.

What is the value of renal biopsy in clinicopathologic correlations in diagnostic and prognostic of glomerular diseases?

A large degree of **proteinuria** (more than 3 g/24 h) is related to lesions in the capillary wall with patent capillary luminal and normal or near-normal glomerular filtration rate. Overall thickening of the glomerular basement membrane (as in membranous nephropathy) or the entire capillary wall (as in mesangiocapillary glomerulonephritis) is invariably associated with proteinuria. Proteinuria may be pronounced in conditions with thin glomerular basement membranes such as minimal change nephropathy or postinfectious glomerulonephritis⁽³⁸⁾.

Significant **hematuria** is more likely to correlate with the severity of proliferative and inflammatory lesions than to sclerotic changes in the glomeruli⁽³⁸⁾.

Severe **oliguria** or even **anuria** correlates

better with the degree of glomerular and vascular damage, but there is no good correlation between the degree of tubular or interstitial changes and urine output⁽⁴⁰⁾.

Interstitial **infiltration of leukocytes** is common in glomerular diseases; interstitial **infiltration of mononuclear** cells contributes to the expansion of the interstitial space⁽⁴¹⁾. The interstitial infiltration by mononuclear inflammatory cells but not glomerular infiltration by these cells correlated with decline of renal function⁽⁴¹⁾.

Activated interstitial mononuclear cells are capable of producing secretion of **cytokines** and growth factors, which are implicated in the pathogenesis of glomerulonephritis. Tubular cells, induce to express HLA-DR antigen ICAM -1 and C5b-9 and can be a source of vasoactive peptides, growth factors and collagen; all these factors may contribute to the tubulo-interstitial damage and renal fibrogenesis, which is the end-point of tubulo-interstitial inflammation. The intensity of this expression in renal tissue is well correlated with the short and long term outcome of renal function in various forms of human glomerulonephritis.

Measurement of these factors in the urine may be a simple and useful mean for the clinician to follow the activity and the progression of the renal disease or its therapeutic response.

Active lesions	Chronic lesions
Proliferation of cells	Glomerulosclerosis
Necrosis	Fibrous crescent
Cellular crescent	Tubular atrophy
Edema	Interstitial fibrosis
Active inflammation	Vascular sclerosis
Glomerulitis	
Interstitial nephritis	
Tubulitis	
Vasculitis	

Table 1. Active and chronic nature of lesion in renal pathology

	Common conditions	Other associated findings
Capsular basement membrane thickening	Diabetes mellitus Renal ischemia Periglomerular fibrosis	Can be as capsular drop Other signs of renal ischemia Features of chronic tubulointerstitial damage
Epithelial cell changes		
Proliferation	Crescentic nephritis	See details below
Metaplasia	Diabetes AKI	Other changes of diabetes Changes of recovering AKI
Capsular space		
Dilatation	Ischemia to glomerulus Mesangiolysis	
Obliteration	Glomerulonephritis Crescent or necrosis Proteinous material in space	

AKI: Acute kidney injury

Table 2. Common abnormalities in relation to glomerular capsule

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Conclusions

Kidney biopsy is an indispensable tool for current practice of evidence-based medicine. The clinicopathologic correlation is a great challenge for both pathologists and nephrologists. Light microscopic examination, immunofluorescence, and electron microscopy should be done routinely in all biopsies. Kidney biopsy, appropriately processed and interpreted, will yield the correct clinicopathologic diagnosis, leading to the appropriate therapeutic strategy while, at the same time, providing key prognostic information.

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	Common conditions	Other associated findings
Thick GBM		
Negative IF	Diabetic nephropathy	EM-Lamina densa thick
	Chronic thrombotic microangiopathy	Silver stain no splitting
	Hereditary nephritis	Silver stain splitting of GBM
		Silver stain irregular
		EM basket weaving
Positive IF	Membranous nephropathy	Spike by silver stain
	Membranoproliferative glomerulonephritis	Subepithelial deposits by EM
		Silver stain GBM splitting
	Amyloid	Subendothelial deposits by EM
		Positive light chains depending on type of amyloid
	Fibrillary glomerulonephritis	Variable splitting by silver
		Fibril by EM
Thin GBM	Alport's syndrome	Silver stain irregular
		EM basket weaving
	Benign familial Hematuria	Thin GBM on EM

GBM: Glomerular basement membrane, EM: Electron microscopy,
IF: Immunofluorescence

Table 3. Common abnormalities in glomerular basement membrane

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