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MINIREVIEWS

Renal biopsy: Still a landmark for the nephrologist

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Abstract

Renal biopsy was performed for the first time more than one century ago, but its clinical use was routinely introduced in the 1950s. It is still an essential tool for diagnosis and choice of treatment of several primary or secondary kidney diseases. Moreover, it may help to know the expected time of end stage renal disease. The indications are represented by nephritic and/or nephrotic syndrome and rapidly progressive acute renal failure of unknown origin. Nowadays, it is performed mainly by nephrologists and radiologists using a 14-18 gauges needle with automated spring-loaded biopsy device, under real-time ultrasound guidance. Bleeding is the major primary complication that in rare cases may lead to retroperitoneal haemorrhage and need for surgical intervention and/or death. For this reason, careful evaluation of risks and benefits must be taken into account, and all procedures to minimize the risk of complications must be observed. After biopsy, an observation time of 12-24 h is necessary, whilst a prolonged observation may be needed rarely. In some cases it could be safer to use different techniques to reduce the risk of complications, such as laparoscopic or transjugular renal biopsy in patients with coagulopathy or alternative approaches in obese patients. Despite progress in medicine over the years with the introduction of more advanced molecular biology techniques, renal biopsy is still an irreplaceable tool for nephrologists.

Key words: Renal biopsy; Acute kidney injury; Bleeding; Haematuria; Hematoma; Chronic renal failure

Core tip: Percutaneous renal biopsy is an irreplaceable tool in the clinical practice of nephrologists to determine diagnosis, prognosis and treatment of several kidney diseases. This procedure is considered safe if it is performed in well-trained centers. Main indications are acute glomerulonephritis and nephrotic syndrome. Since bleeding is the major primary complication, careful evaluation of risks and benefits must be considered. The risk of complications in patients with coagulopathy may be reduced by using laparoscopic or transjugular renal biopsy or alternative approaches in obese patients. Despite progress in medicine over the years, renal biopsy is still an irreplaceable tool for nephrologists.

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INTRODUCTION

Percutaneous renal biopsy (PRB) is still considered an irreplaceable tool for diagnosis, prognosis and choice of treatment of several primary or secondary kidney diseases. The indications uniformly recognized by most nephrologists are represented by nephritic and/or nephrotic syndrome and unexplained acute or rapidly progressive renal failure[1]. Primary glomerulonephritis are the more common renal disease in renal biopsy registries. Among them IgA nephropathy (IgAN) is the most frequent renal diagnosis. Regarding systemic diseases, systemic lupus erythematosus (SLE) is the most frequent indication for PRB, because this last determines the level of activity and/or chronicity of the lesions and the reversibility of renal lesion as a result of therapy. PRB can also be helpful in vasculitis to assess the severity of the damage and the potential reversibility after therapy. In diabetes the use of PRB is motivated by a relatively recent or very late appearance of proteinuria > 1 g and/or a rapid decline in GFR and/or active urinary sediment, in the absence of other signs of microangiopathy (retinopathy and neuropathy); in fact, in these patients primitive forms of glomerular diseases are frequently reported, superimposed or not to the typical lesions of diabetes. In advanced chronic renal failure, PRB is useful to assess a rescue therapy or to know the causal nephropathy in view of renal transplantation[2].

PRB is also an informative procedure in renal transplantation, both in the postoperative, for the differential diagnosis of acute rejection *vs* other diseases, and in follow-up of organ transplantation for differential diagnosis between recurrence of primary renal disease, development of glomerulonephritis *ex novo*, and acute or chronic rejection (Table 1).

Table 1 List of Indications for renal biopsy

Nephrotic syndrome
Acute kidney injury (when rule out obstruction, and pre-renal causes)
Systemic disease with renal dysfunction (in diabetic patients only if it presents with atypical features)
Non-nephrotic proteinuria, and in some circumstances isolated microscopic hematuria
Unexplained chronic kidney disease
Familial renal disease (may avoid biopsy in other family members affected)
Renal transplant dysfunction

HISTORY

The first renal biopsy of native kidney was performed in 1901 in a surgical procedure for renal decapsulation in the treatment of a Bright's syndrome[3]. The PRB was born in 1944 when Nils Alwall adapted a technique for percutaneous liver biopsy in the kidney, using an aspiration needle technique[4] with a radiographic procedure for the localization of the right kidney and keeping the patient in a sitting position. With this innovative method, he obtained adequate tissue in ten of the thirteen patients[5]. However, this procedure has been for the first time described in the literature by Iversen and Brun[6] in 1951, which also used an aspiration needle and the sitting position but, in contrast to Nils Alwall, they used intravenous pyelography for localization of the right kidney; unfortunately they obtained adequate tissue only in 53% of patients[6]. Given the poor results of this technique, Kark *et al*[7] in 1954 made significant changes including the prone position of the patients with a sandbag placed under the abdomen to reduce the mobility of the kidney and the introduction of a new type of needle, the Franklin-modified Vim-Silverman needle, which trapped the tissue in the needle and then sheared it off, achieving adequate tissue in 96% of patients and no major complications. To localize the lower pole of the kidney they used as landmark the distances between the vertebral spinous processes and the 11th and 12th ribs, and the movement of a finder needle following a deep inspiration[7]. Over the years the technique has been improved more and more, increasing the adequacy of the sample and reducing the risk of complications.

In 1962 the use of radiological images was introduced for the localization of the kidney, later replaced by the ultrasound real-time imaging. Since then this procedure, which was initially performed by nephrologists, has gradually become a prerogative of radiologists. In fact, between 1964 and 1974 the PRB was performed in 95% of cases by nephrologists[8], while in 1980s the number of nephrologists who performed the PRB was gradually reduced in favour of radiologists and in 2011, Lane *et al*[9] showed that radiologists were the main performers of this technique (Figure 1)[10].

A recent european survey stated that in 60% of the centers renal biopsy is performed by nephrologysts, in 30% by radiologists and in 5% by nephrologysts and radiologists[11]. Today, the standard procedure for PRB involves the use of real-time ultrasound and automated spring-loaded biopsy device[12].

NEEDLE TYPES AND SIZE

There are different types of biopsy needles and the first used was an aspiration needle, subsequently replaced by the cutting Vim-Silverman needle, which trapped the tissue in the needle and then sheared it off. The evolution of the latter is the Tru-Cut needle, which is a manually operated sheathed needle designed for manual capture of high-quality tissue samples with minimal trauma to the patient. Today it is replaced by automatic spring-loaded biopsy guns and semi-automatic biopsy guns with

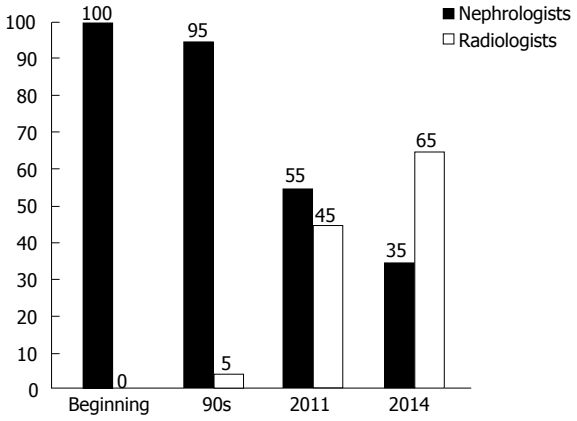

Figure 1 Rate of performers (nephrologists and radiologists) of renal biopsy along the course of the years[10].

better and safer performance.

The optimal needle size for native renal biopsies has not been established, but the most used are three: 18 gauge (internal diameter 300-400 μm), 16 gauge (internal diameter 600-700 μm) and 14 gauge (internal diameter 900-1000 μm). The first one is reserved to paediatric patients because the internal diameter of the needle is barely bigger than an adult glomerulus (200-250 pmol/L), while the other two are more appropriate for the adult patients[13,14]. On the other hand, the length of this device is almost the same and is around 20 cm.

SAMPLE ADEQUACY

The number of glomeruli is the main determinant of the biopsy adequacy but it varies based on the type of glomerular disease. For example in focal disease, such as focal segmental glomerulosclerosis, the diagnosis can be made by identifying even one glomerulus that presents the typical lesions but the probability to make diagnoses is directly proportional to the number of glomeruli[15]. Therefore, in a kidney in which 20% of glomeruli are sclerotic, if a bioptic sample includes five glomeruli the probability to miss affected glomeruli is about 35%. This percentage falls down to 10% if the bioptic sample includes ten glomeruli and to 1% if it includes twenty glomeruli[16,17]. Therefore, the minimum number of glomeruli required to define an adequate bioptic sample is ten, and usually, to get this target at least two different cores are taken which are divided for light microscopy (LM) (placed in formalin or another fixative), immunofluorescence (IF) (placed in transport solution-saline solution- and quickly freezed), and electron microscopy (EM) (fixed in 2%-3% glutaraldehyde or 1%-4% paraformaldehyde)[18].

Actually, the latter is not frequently and widespread performed in the practice of renal biopsy since it is possible to get a diagnosis in most cases with the contribution of the LM and the IF. However, due to the relevance of EM in some specific glomerular diseases, it has been recommended that renal tissue for EM be set aside in each case if EM cannot be performed routinely[19]. As an alternative, IF may be also performed on paraffin sample, using only one core for LM and IF and further reducing the risk of complications resulting from biopsy. The technique is certainly more complicated and needs more time for preparation but provides comparable results with the classic procedure with the exception of complement factors; consequently, it may be used in selected cases and/or in patients with greater bleeding risk.

About the optimal needle size for native renal biopsies, there is not a general consensus to achieve a good compromise between sample adequacy and lower number of complications. In adult patients a 14 or 16 gauge needle seems to be appropriate[20], while in paediatric patients it is better to use 18 gauge needles[21].

COMPLICATIONS

Even if PRB is considered a safe procedure, it is not without complications (Table 2) that, in very rare cases, may also cause death or require extreme procedures such as nephrectomy[22-24]. For this reason it is always necessary to evaluate the risk/benefit for the patient, inform him/her and obtain a signed consent. Furthermore, complications are divided into major complications that need a treatment or an intervention to stop the problem, and minor complications that spontaneously resolve without intervention or further treatment; in both cases, bleeding is the main consequence of PRB and can occur at different levels: (1) in the collecting duct system, causing micro - gross haematuria which may result in clots formation in the urine (ureter or bladder) with risk of obstructive renal failure; (2) below the kidney capsule, causing subcapsular hematoma formation that in rare cases may lead to the Page kidney, which consists in renal ischemia caused by prolonged compression of the kidney from haemorrhage with resulting arterial hypertension characterized by high renin levels[25]; and (3) in the perinephric space, causing hematoma formation which may be asymptomatic, in the majority of cases, or result into a clinically relevant complication, such as lumbar pain, significant drop in haemoglobin concentration, or need for a blood transfusion.

However, the risk of complications after renal biopsy is not high (Table 3). In fact, in a systematic review and meta-analysis of 34 retrospective and prospective studies including 9474 adult patients who underwent biopsy of the native kidney, using ultrasound real-time imaging and automatic biopsy device, the overall incidence of bleeding complications were: Transient gross haematuria 3.5%, request for transfusion therapy 0.9%, demand on angiographic control of bleeding 0.6%, request for nephrectomy for control of bleeding 0.01% and death 0.02%[26]. Thus, the risk of using invasive procedures to stop bleeding is very rare[27,28]. More frequently we can treat this complication with medical treatment such as administration of endovenous fluid and/or blood products[29]. Moreover in some cases of persistent hemorrhage, before

Table 2 Types of complications after renal biopsy

Minor complications	Major complications
Bleeding	Bleeding
Asymptomatic haematoma	Hematoma requiring blood transfusion or invasive procedure to stop bleeding
Microscopic and gross haematuria	Urinary tract obstruction with or without AKI
Anaemia (drop in haemoglobin concentration ⩾ 1 g/dL)	Hypotension related to bleeding
Pain (> 12 h)	Nephrectomy
Page kidney	Sepsis
Perinephric infection	Other organs and/or blood vessels perforation
Arteriovenous fistula	Death

AKI: Acute kidney injury.

Table 3 List of main studies (> 500 biopsies) reporting minor, major complications and mortality rate after renal biopsy

Ref.	Year of publication	No. of biopsies	% Minor complications	% Major complications	% Mortality
Fenerberg *et al*[24]	1998	1081	9.6	1.11	0.09
Prasad *et al*[28]	1998	1090	3	0.36	0
Preda *et al*[20]	2003	515	9.5	2.7	0
Whittier *et al*[51]	2004	750	6.7	6.4	0.13
Atwell *et al*[44]	2010	5832	-	0.7	0
Stratta *et al*[29]	2007	1137	24.2	0.36	0
Korbet *et al*[23]	2014	1055	8.1	6.6	0.09
Mai *et al*[21]	2013	934	5.9	0.86	0
Tøndel *et al*[13]	2012	9288	1.9	0.9	0
Prasad *et al*[28]	2015	2138	5.4	5.1	0

performing embolization of a pseudoaneurysm or surgery to stop the bleeding, we can resort to off-label drug use such as recombinant activated factor Ⅶ[30].

Specific symptoms and signs post-biopsy

Lumbar pain: The pain is an extremely common consequence of PRB and usually occurs at the end of anaesthesia. If necessary it is possible to administer a mild analgesic. Otherwise, the onset of greater pain suggests the development of a major complication and further diagnostic tests must be performed.

Microscopic haematuria: It is the most common consequence of this procedure; it is usually asymptomatic[31] and resolves spontaneously over a few days.

Gross haematuria: It occurs in 3% of renal biopsies and typically disappears in few hours or days. Occasionally gross haematuria may cause a significant drop in haemoglobin concentration requiring a blood transfusion or, in rare cases, it may result in clots formation with or without obstructive renal failure. On the contrary, persistent haematuria after three days suggests the onset of major complications such as arteriovenous fistula (AVF)[32].

Acute anaemia: A decrease of haemoglobin concentration ⩾ 1 g/dL occurs in more than 50% of uncomplicated renal biopsies[33], whereas a fall ⩾ 2 g/dL occurs in 10% of uncomplicated cases and is consequently associated with increased risk of complications[34].

Perinephric hematoma: The presence of asymptomatic hematoma is frequently detected during a renal ultrasound after biopsy and does not constitute *per se* a complication. Prospective studies showed that perinephric hematoma is detectable in 90% of patients 24-72 h after the procedure, while this percentage drops to 15% immediately after the biopsy. Most of the perinephric hematomas are small, asymptomatic and they resolve spontaneously in few months; only in 2% of cases they may cause a clinically relevant complication such as lumbar pain, a decrease in haemoglobin concentration, or the need for blood transfusion. However, the absence of hematoma at 1 h was highly predictive of an uncomplicated course[35].

Waldo *et al*[36] showed that patients which did not present perinephric hematoma one hour after biopsy did not develop major complications in 95% of cases, while the presence of hematoma was predictive for major complications in 43%. Therefore, the routine use of ultrasound at 1 h after PRB may have a role in determining an uncomplicated course[36].

AVF: It is not a frequent complication and is due to trauma of the wall of blood vessels; it is clinically asymptomatic and resolves spontaneously in most cases[37]. In rare cases AVF can cause the development of an aneurysm, which may manifest clinically with high

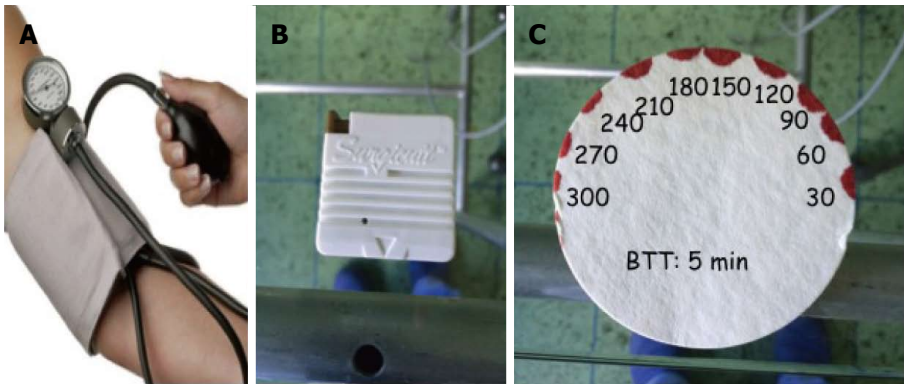

Figure 2 Bleeding time procedure. A: Place the sphygmomanometer on the upper arm and inflate to 40 mmHg; B: Make a small cut on the lower arm with automatic standard device; C: Blotting paper is used to draw off the blood every 30 s (normal range 3-7 min).

blood pressure, heart failure, and kidney failure. Important signs that suggest this complication are the persistence of gross haematuria, the presence of abdominal bruit and palpable trill[38,39] but diagnosis confirmation requires Doppler ultrasound or magnetic resonance imaging, or angiography. The treatment of symptomatic cases is based on superselective transcatheter arterial embolization or, in rare cases, surgery[40].

CONTRAINDICATIONS AND RISK FACTORS

Contraindications to renal biopsy and risk factors must be taken into account to minimize the risk of complications.

The presence of intravascular coagulopathy, polycystic kidneys, obstruction of the urinary tract, hydronephrosis, infections of the upper urinary tract are regarded as absolute contraindications. Otherwise, there are some conditions, which require caution, considered as relative contraindications, such as compromised cardiopulmonary function or hemodynamic instability, severe obesity, inability of the patient to cooperate, solitary kidney, advanced age, severe hypertension (> 160/95 mmHg), and renal failure[41]. The last one causes functional alterations of coagulation factors as the von Willebrand factor (vWF) and the Factor Ⅷ, abnormalities in platelet membrane, accumulation of uremic toxins that inhibit platelet aggregation, high levels of prostacyclin and nitric oxide which are factors that reduce platelet aggregation. Another element that often contributes to increase the risk of bleeding in renal failure is the presence of anaemia. Other diseases associated with greater risk of bleeding are those with arteriolar involvement as SLE, vasculitis, scleroderma, amyloidosis and advanced diabetic nephropathy because they interfere with the first mechanism of haemostasis, known as the vascular phase, reducing the arteriolar contraction.

PROCEDURES PRE-BIOPSY

Before performing the PRB it is very important to follow some recommendations to minimize the risk of complications. Renal ultrasound is essential to evaluate the presence of anatomical abnormalities of the kidney (presence of multiple cysts, hydronephrosis, solitary kidney) that may represent a risk factor for the development of complications.

Laboratory tests may reveal the potential presence of coagulopathy. To totally assess the steps of haemostasis it is useful to use the bleeding time that evaluates the time of platelet aggregation (Figure 2). In case of advanced renal failure and/or prolonged bleeding time, the administration of desmopressin acetate - DDAVP (0.3 μg/kg), estrogen and cryoprecipitate has shown a reduction of the bleeding risk[42,43].

Antiplatelet agents and oral anticoagulants have to be withdrawn at least one week before renal biopsy[44], the last ones until normalization of INR, and replaced with low molecular weight heparin (LMWH). Other drugs that may cause alterations in coagulation are the non-steroidal anti-inflammatory drugs (NSAIDs), which should be not taken for at least 5 d before PRB.

ALTERNATIVE APPROACHES FOR RENAL BIOPSY

In some cases, PRB may be contraindicated because of bleeding diatheses or habitus of the patients such as obesity. In these circumstances we can perform renal biopsy with alternative methods such as under CT guidance[45] or with laparoscopic[46] and transjugular approach[47]. These techniques may have some limits. CT guidance, for example, does not assess any possible movements of the kidney related to breathing, laparoscopic biopsy requires general anaesthesia and transjugular biopsy seems to be associated with a lower diagnostic power due to the need to pass through the medulla first[48].

In obese patients a new approach of PRB under real-time ultrasound guidance has been proposed with the patient in supine antero-lateral position (SALP). Gesualdo *et al*[49] reported a case series of 110 patients undergoing PRB, divided into two groups: Low risk group (90 patients) if the body mass index (BMI) was ⩽ 30 in the absence of respiratory disorders and high risk group (20 patients) if BMI was > 30 with breathing problems. The first group underwent classical PRB in prone position and the other group in SALP, demonstrating, at the end of the study, that there were no substantial differences about adequacy samples and patients safety[49]. Moreover, an open renal biopsy may be performed when uncorrectable

contraindications are present. Nomoto *et al*[50] reported 931 cases of open kidney biopsies concluding that this is a safe procedure with 100% of sample adequacy but an important limitation of this technique is the use of general anesthesia.

PERIOD OF OBSERVATION

After biopsy, the patient must be at rest for at least 6-8 h in the supine position. Blood pressure should be monitored frequently, and urine must be checked to evaluate the presence of gross haematuria. If there are no signs of bleeding within 6 h, the patient may sit up, because most of complications occur within 6-8 h. However, since some complications may also occur later, the ideal observation time should be continued for 24 h. In a case series of 750 biopsies of native kidney it was reported that 67% of major complications appeared within the first 8 h, suggesting that observation for 24 h is safer in renal biopsy[51].

CONCLUSION

PRB is a safe procedure and the risk of development of major complications is very rare. Instead, the minor consequences due to the procedure occour more frequently. These are micro- and/or gross haematuria, drop in hemoglobin concentration > 1 g/dL, development of asymptomatic perinephric hematoma. All these minor adverse events can be more safely managed and do not bring particular complications to the patient. It is mandatory to identify risk factors for bleeding such as anaemia, prolonged bleeding time or advanced renal failure, severe arterial hypertension and correct them when possible; where this is not possible, it is recommended to postpone the procedure.

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