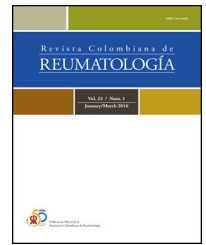




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## Editorial

# Is the renal biopsy still necessary in lupus nephropathy?☆



## ¿Sigue siendo necesaria la biopsia renal en la nefropatía lúpica?

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Lupus nephropathy (LN) is one of the most frequent and devastating manifestations of systemic lupus erythematosus (SLE). It affects more than a half of patients with this disease and it is characterized by the development of inflammatory damage of the nephrons, which is expressed in various anatomopathological types.<sup>1-4</sup> The damage during acute inflammation is rapid, but potentially reversible with immunosuppressive treatment; instead, chronic lesions such as tubular atrophy and fibrosis, do not improve with this treatment and lead to chronic renal failure.

For many years the renal biopsy (RB) has remained as the gold standard for the diagnostic approach of the patients with suspected LN. According to the criteria of the Systemic Lupus International Collaborative Clinics group,<sup>5</sup> the presence in the RB of a lesion indicative of LN, together with the positivity of antinuclear or anti-double-stranded DNA antibodies, is sufficient to classify a patient as having an effect of SLE. However, some experts call into question the need for RB in

LN or suggest its limited use. In clinical practice, in the face of the concerns of both physicians and patients in relation to safety, the question arises: Is the renal biopsy still necessary in lupus nephropathy? In this editorial we will analyze the main postulates about this question.

The clinical and anatomopathological diversity of LN makes difficult the development of an algorithm for its diagnosis and treatment. The majority of experts recommend the performance of RB to all patients in whom there is a clinical suspicion of active LN, unless strictly contraindicated. The RB should be done before starting an immunosuppressive treatment, preferably within the first month following the discovery of the laboratory alterations suggestive of LN.<sup>6-10</sup> RB allows to classify the anatomopathological findings in various types of LN and to define the activity and chronicity indexes. In 2003, the International Society of Nephrology/Renal Pathology Society proposed the existing classification for LN.<sup>11</sup> It is required to visualize at least 10 glomeruli so that the

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anatomopathological exam is valuable and to exclude reasonably a focal involvement. The sample of the RB should be examined by light microscopy, immunofluorescence and, if it is possible, by electron microscopy. On the other hand, the vascular and interstitial lesions must be described and the data on activity and chronicity must be quantified.

For the majority of the experts, a proteinuria greater than 500 mg/24 h is the most strong criterion to indicate the performance of RB.<sup>6-9</sup> In patients with a glomerular filtration rate lower than 30 ml/min, but without relevant proteinuria, the indication for RB is doubtful, unless the size of the kidney is normal or there is evidence of active renal disease according to the recommendations of the European League Against Rheumatism and the European Renal Association-European Dialysis and Transplant Association.<sup>6</sup> Conversely, the indications for repeat the RB are controversial and differ among experts. It is usually carried out in patients with recurrent or refractory disease. It is also performed in clinical trials to monitor treatment efficacy. Another problem that arises is the indication of RB in patients with proteinuria lower than 500 mg/24 h.<sup>12</sup> In a study of 38 patients with SLE who had glomerular hematuria and proteinuria lower than 500 mg/24 h, the first RB revealed in 95% of cases class III and IV lesions and only 5% had class II lesions.<sup>13</sup> These data show that the classification of LN should not be based only in laboratory parameters, as this may result in incorrect therapeutic decisions.

Some recent clinical data suggest that the administration of mycophenolate mofetil associated with glucocorticoids could be the first choice treatment in all patients with severe forms of LN (classes III, IV and V),<sup>6</sup> which would avoid having to differentiate between the diverse anatomopathological types of LN; however, this attitude is not risk-free. Proteinuria or active urinary sediment not only occur in the context of SLE but they also may appear in other glomerular diseases such as, for example, minimal change nephropathy, focal and segmental glomerulonephritis, amyloidosis, IgA nephropathy or acute tubular necrosis.<sup>14-19</sup> In a series of more than 200 patients with SLE and renal involvement, non-lupus nephropathy could be confirmed in 5% of patients.<sup>16</sup>

On the other hand, the RB allows to determine the degree of activity of LN.<sup>20,21</sup> The activity and chronicity indexes allow to select the patients who require immunosuppressive treatment and those who only will benefit from renal protection such as, for example, dietary salt restriction, strict control of high blood pressure and the use of renin-angiotensin system inhibitor drugs.<sup>22</sup> Likewise, in SLE is frequent the presence of the associated antiphospholipid syndrome (APS). The renal anatomopathological finding of the latter is the presence of glomerular thrombotic microangiopathy, which occurs in up to 30% of patients with SLE, with or without LN.<sup>23-26</sup> The diagnosis of thrombotic microangiopathy cannot be established without RB, because the mere presence of antiphospholipid antibodies is not sufficient.

Much information on the prognostic value of the RB after completing induction treatment comes from clinical trials. Data of RB performed after 6-9 months of induction therapy with immunosuppressants revealed that they are more predictive of the long-term evolution than the RB at the time of diagnosis.<sup>27-29</sup> The glomerular and interstitial inflammation,

the presence of immune complexes in the glomerular capillaries and of macrophages in the tubular lumens in the RB at 6 months of treatment, were predictors of doubling of serum creatinine.<sup>27-29</sup> Other studies indicate that the development of unsatisfactory outcomes in the long-term, such as doubling of serum creatinine, renal failure or death, are related with glomerular and tubulointerstitial inflammation persisting one year or more after induction therapy.<sup>26,27</sup> Some authors postulate that deferring the RB until the end of the induction treatment might be better for the estimation of the prognosis of patients. The question of whether the patients without active changes in RB after the induction therapy need maintenance immunosuppression still remains unanswered.<sup>27,30-32</sup>

Maintenance treatment consists in the administration of mycophenolate mofetil or azathioprine. This treatment should be given for at least 3 years and, in patients with residual disease or without clinical symptoms of active disease, the decision on its cessation should be made with utmost caution. This dilemma is especially important in patients who consider the possibility of pregnancy. The possible persistence of renal inflammatory activity is the main argument against treatment interruption.<sup>33,31,34-36</sup> The repetition of the RB at the end of the maintenance phase in patients who had responded clinically to treatment allows to assess the disease activity before stopping therapy. The rationale for performing these RB is the observation that the LN may still be active after several years of immunosuppression. In these patients, the interruption of immunosuppressive treatment can lead to rapid progression towards chronic renal lesion. This conclusion is reinforced by the fact that one third of patients have a persistent inflammatory lesion or subendothelial immune complexes, despite the complete clinical response. Repeating the RB after the maintenance period not only helps to distinguish the patients with anatomopathological activity, it is also an argument to withdraw safely the immunosuppression in some patients with low-grade proteinuria.<sup>35-37</sup>

Almost all the recommendations of experts include the repetition of the RB in a recurrence of LN.<sup>38-44</sup> However, the decision to repeat the RB, according to some studies, should be based on the class of LN in the initial RB.<sup>44</sup> Non-proliferative LN class II or V in the initial RB may benefit from a repetition of the RB, since these patients have a reasonable possibility to switch to a proliferative form and will require a more aggressive immunosuppressive treatment. In contrast, it may be not necessary to repeat the RB in patients with initial proliferative LN, since they are more prone to confirm the persistent or recurrent proliferative LN which, therefore, would not cause any change in therapy.<sup>45-47</sup>

In conclusion, RB, initial and later in the evolution of each patient, can change the therapeutic approach into another more aggressive, or protect the patients without disease activity against the toxicity of the drugs. So far, the data from the literature allow to state that the performance of the RB provides more advantages than disadvantages.

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