Duplex Doppler Sonography to Predict Response to Therapy in Active Lupus Nephritis

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Abstract

Objective: Duplex Doppler sonography had been applied to examine various renal disorders such as renal allograft rejection, obstructive kidney disease, renovascular hypertension, and parenchymal renal disease.

Materials and methods: The goals of our study were: 1) to evaluate the relationship between resistance index (RI), measured by duplex Doppler sonography, and results of renal biopsy; 2) to determined the value of RI for predicting response to therapy in patients with lupus nephritis. Forty-four patients with initially diagnosis of lupus nephritis was enrolled and duplex Doppler sonography examinations were performed immediately before the renal biopsy. After six months of therapy, predictors of response to therapy were analyzed.

Results: The results showed that 1) the chronicity index (CI) of renal biopsy was significantly higher in 21 patients with increased RI, when compared with 23 patients with normal RI (4.67 ± 2.31 versus 1.74 ± 1.21, \(p<0.001\)); 2) twenty-two patients without response to treatment of immunosuppressive agents had increased RI, when compared with 22 patients with response (0.76±0.12 versus 0.66±0.07, \(p=0.001\)); 3) increased RI was significantly associated with an increased likelihood of poor response to treatment according to stepwise regression model.

Discussion: The present study demonstrates the RI of duplex Doppler sonography had a good correction with CI of renal biopsy and could predict response to treatment.

Key words: Lupus, Resistance index, Chronicity index.

Introduction

Lupus nephritis is the most common form of visceral organ involvement in systemic lupus erythematosus (SLE). Lupus nephritis has been reported in 40%-75% of patients with SLE (1,2). Renal involvement is a leading cause of morbidity and mortality from SLE. Lupus nephritis is extremely heterogenous both clinically and pathologically, and flares and remissions of diseases are usually

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associated with therapy (3,4). It is therefore important to identify prognostic indicators to facilitate the formulation of appropriate management plans. There have been a large number of studies evaluating the prognosis of lupus nephritis over the past three decades. In general, these studies have evaluated clinical, laboratory or biopsy features at the onset of study. No research has been done to evaluate the potential of duplex Doppler sonography as a predictor of response to treatment.

The most important survey of lupus nephritis is histological assessment by renal biopsy. Clinicians usually select appropriate therapy according to the results of renal biopsy. However, since renal biopsy is an invasive procedure, a non-invasive alternative would have clinical benefits. The use of duplex Doppler sonography to examine various renal disorders such as renal allograft rejection (5), obstructive kidney disease (6), renovascular hypertension (7), and parenchymal renal disease (8) have been reported. The goals of our study were: 1) to evaluate the relationship between resistance index (RI), measured by duplex Doppler sonography, and results of renal biopsy; 2) to determine the value of RI for predicting response to therapy inpatients with lupus nephritis.

**Materials and Methods**

Forty-four patients with initial diagnosis of SLE (40 women and 4 men, mean age 24.6 yr.) were enrolled in the study. These patients were satisfied diagnostic criteria for SLE established by the American Rheumatism Association (9), and underwent renal biopsy procedures and were proven to have type IV lupus nephritis according to World Health Organization (WHO) guidelines (10).

Renal biopsies were performed and evaluated using standard methods. There are no definite criteria for the performance of renal biopsy in SLE patients at present. In Taichung Veterans General Hospital, mostly, we do renal biopsy in cases with situations such as initial diagnosis, treatment failure, second flare of disease, and rapid deterioration of renal function. Based on biopsy results, we recruited patients with type IV lupus nephritis. The activity and chronicity indices of renal pathology were calculated based on the system developed by Pirani and colleagues (11) and later modified by Austin and colleagues (12). Activity index (AI) was defined as the sum of the individual scores of 6 features (glomerular cell proliferation, leukocyte exudation, karyorrhexis, fibrinoid necrosis, cellular crescents, hyaline deposits, and interstitial inflammation) considered to represent measures of active lupus nephritis. Chronicity index (CI) was defined as the sum of the individual scores of 4 features (glomerular sclerosis, fibrous crescents, tubular atrophy, and interstitial fibrosis) considered to represent measures of chronic irreversible lupus nephritis. Each individual component was scored 0 (normal), 1, 2, or 3 (severe abnormality). The maximum AI value is 18 points and the maximum CI value is 12 points. The WHO classification, AI, and CI were determined by two pathologists, who had no prior knowledge of specimen source.

In each patient, both kidneys were examined with real-time ultrasound (US) with a 3.75-MHz transducer (Toshiba PVF-375 MT) Pulsed Doppler US evaluation of the intrarenal arteries was obtained at the same respective scanning frequencies. All US examinations were performed immediately before the renal biopsy. Doppler signals were obtained from
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interlobar arteries along the border of medullary pyramids. The resistance index (RI, [peak systolic frequency shift−minimum diastolic frequency shift]/ peak systolic frequency shift) was calculated from the hard-copy image by means of manual measurement with calipers. All measurements were performed by the same examiner, who was blinded to laboratory and biopsy results. Three different interlobar arteries from each kidney was randomly selected and examined, and a mean value from the two kidneys was calculated.

The patients received immunosuppressive agents for six months after renal biopsy. After six months of therapy, predictors of response to treatment were analyzed.

For purposes of data analysis, a RI of greater than or equal to 0.7 was considered abnormal. After treatment proteinuria decreased to less than 0.2 g/day was defined as total remission, and proteinuria decreased to less than half of previous proteinuria was defined as partial remission.

Statistical Analysis

The statistical significance of differences between groups was evaluated using student’s t-test. Multiple regression analysis was performed on the basis of renal outcome. Values are expressed as the mean±SD. P values less than .05 were considered significant.

Results

The laboratory data and results of renal biopsy, according to the findings of RI are shown in Table I. Twenty-one of 44 patients had increased RI (>0.7) and twenty-three patients had normal PI. About the correlation between RI and pathology, the CI was significantly higher in patients with increased RI, when compared with patients with normal RI (4.67 ± 2.31 versus 1.74 ± 1.21, p<0.001); but RI was not related to AI (2.52 ± 1.25 versus 2.32 ± 1.08, p=0.85). Besides, the patients with increased RI and those with normal RI had similar laboratory data, including serum creatinine, anti-dsDNA antibody titer, and daily urinary proteinuria. Therefore, the above findings suggest that increased RI can reflect severity of renal pathology in lupus nephritis.

All patients received a combined therapy of monthly intravenous cyclophosphamide and oral prednisolone for six months. After six months of treatment, twenty-two patients experienced complete or partial remission. Lupus patients without remission had significantly increased RI and CI, compared with those without remission (RI: 0.76±0.12 versus 0.66±0.07, p=0.001; CI: 4.16±2.11 versus 1.91±1.87, p=0.001) (Table II).

To detect the predictor of response to treatment in lupus patients, multiple regression analysis of multiple study parameters was performed and shown in Table III. Stepwise regression revealed RI and chronicity index were statistically significant independent predictors.
### Table 1. The relationship between Resistance Index (RI) and laboratory data, and results of renal biopsy

<table>
<thead>
<tr>
<th></th>
<th>RI &lt; 0.7 (n=23)</th>
<th>RI ≥ 0.7 (n=21)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity Index</td>
<td>2.12±1.08</td>
<td>2.52±1.25</td>
<td>0.255</td>
</tr>
<tr>
<td>Chronicity Index</td>
<td>1.74±1.21</td>
<td>4.67±2.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti-dsDNA (IU/mL)</td>
<td>76.00±55.96</td>
<td>98.95±60.80</td>
<td>0.199</td>
</tr>
<tr>
<td>Daily urine proteinuria (g/day)</td>
<td>2.43±1.07</td>
<td>2.54±1.03</td>
<td>0.869</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>1.54±0.51</td>
<td>1.98±0.94</td>
<td>0.070</td>
</tr>
</tbody>
</table>

### Table 2. The relationship between response to therapy and multiple parameters

<table>
<thead>
<tr>
<th></th>
<th>No Response (n=22)</th>
<th>Response (n=22)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>RI</td>
<td>0.66±0.07</td>
<td>0.76±0.12</td>
<td>0.001</td>
</tr>
<tr>
<td>Activity Index</td>
<td>2.59±1.26</td>
<td>2.45±1.06</td>
<td>0.699</td>
</tr>
<tr>
<td>Chronicity Index</td>
<td>1.91±1.87</td>
<td>4.16±2.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti-dsDNA (IU/mL)</td>
<td>84.09±67.67</td>
<td>89.82±49.80</td>
<td>0.751</td>
</tr>
<tr>
<td>Daily urine proteinuria (g/day)</td>
<td>2.38±1.07</td>
<td>2.50±1.03</td>
<td>0.711</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>1.58±0.69</td>
<td>1.92±0.82</td>
<td>0.137</td>
</tr>
</tbody>
</table>

### Table 3. Results of regression analysis of multiple parameters in the prediction of response to immunosuppressive therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression coefficient</th>
<th>SE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RI</td>
<td>9.982</td>
<td>6.297</td>
<td>0.005</td>
</tr>
<tr>
<td>Activity Index</td>
<td>-0.5867</td>
<td>0.5214</td>
<td>0.2605</td>
</tr>
<tr>
<td>Chronicity Index</td>
<td>0.403</td>
<td>0.294</td>
<td>0.026</td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>-0.0028</td>
<td>0.0083</td>
<td>0.7406</td>
</tr>
<tr>
<td>Daily urine proteinuria</td>
<td>0.3079</td>
<td>0.4174</td>
<td>0.4608</td>
</tr>
<tr>
<td>Cr</td>
<td>-0.1077</td>
<td>0.5804</td>
<td>0.8528</td>
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</table>
Discussion

We used duplex Doppler sonography to examine intrarenal hemodynamic changes noninvasively in patients with lupus nephritis. We demonstrated that RI of duplex Doppler sonography has a good correlation with CI of renal biopsy and can predict response to treatment for lupus nephritis. Therefore, duplex Doppler sonography may be a useful alternative to renal biopsy in predicting the severity of renal pathology of lupus nephritis.

Use of conventional US has been previously reported in the evaluation of lupus nephritis (13). Abnormalities of renal size and cortical echogenicity have been reported. However, many patients with documented renal involvement from SLE will have completely normal conventional US examination. Conventional US does not typically provide an additional predictive clinical information over the traditional serologic and biopsy parameters.

The blood-flow-velocity waveform contains information about the velocity of every blood cell within the blood vessel under interrogation by the ultrasound beam. Since RI is ratio, that is independent of angle between the ultrasound beam and blood vessels. Increases in downstream resistance result in a relative reduction in diastolic flow compared with systolic flow and elevation of the RI. Hence, the RI can be used as an estimate of the state of renal arterial resistance (14). The use of duplex doppler sonography to examine various renal disorders such as renal allograft rejection (5), obstructive kidney disease (6), renovascular hypertension (7), parenchymal renal disease (8), glomerulonephritis (15), and diabetic nephropathy (16) have been reported. There were two previous studies about duplex Doppler sonography in lupus nephritis (17,18). The first article demonstrated that RI was not correlated with histopathologic findings, but there were only nine renal biopsy specimens. The second article revealed that patients with elevated RI had significantly higher CI according to survey of 32 renal biopsy specimens. Our results also support the findings. Furthermore, we try to use RI to predict the response to treatment for lupus nephritis.

RI correlated the chronicity index of renal biopsy in lupus nephritis in our study.

RI was correlated with histopathologic findings to gain information about the causes of increased vascular resistance in renal parenchymal disease. Previous studies (8,19,20) suggest that RI elevation is more likely to occur with a vascular or tubulointerstitial renal process, and is much less likely with disease only limited to the glomeruli. Almost all patients with pure glomerular disease have relatively normal RIs unless the disease is end stage or there are associated tubulointerstitial or vascular pathological changes. Platt et al (19) demonstrated that RI was more associated with the biopsy presence of chronic irreversible lesions in particular located within the interstitium of the kidney. Mostbeck et al (20) reported there was a correlation between the RI and the degree of arteriosclerosis, glomerular sclerosis, glomerular sclerosis, arteriosclerosis, interstitial edema, and interstitial fibrosis, but no correlation between the RI and the degree of glomerular cell proliferation, and leukocytic infiltration. Chronicity index consists of glomerular sclerosis, fibrous crescents, tubular atrophy, and interstitial fibrosis. Activity index consists of glomerular cell proliferation, leukocyte exudation, karyorrhexis, fibrinoid necrosis, cellular crescents,
hyaline deposits, and interstitial inflammation. The above findings can explain why increased RI is associated with higher CI, but not AI. Therefore, increased RI could reflect more severe chronicity of renal pathology in lupus nephritis, which meant more irreversible lesions.

CI score had been found to be important predictor of long-term outcome in lupus nephritis (21,22). Several studies demonstrated that tubulointerstitial lesions as the major locations of injury for determining prognosis in lupus nephritis (1,21,23). The severity of interstitial disease correlated with the degree of renal insufficiency and was a valuable marker for progressive deterioration in renal function (24). Therefore, the predictive value of RI is likely to resulted from the correlation of RI with CI and tubulointerstitial changes.

In conclusion, the present study demonstrates that duplex Doppler sonography is useful in the noninvasive assessment of intrarenal hemodynamic abnormality present in lupus nephritis. We demonstrate the RI of duplex Doppler sonography had a good correction with CI of renal biopsy and could predict response to treatment.

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都卜勒超音波用於預測狼瘡性腎炎的療效

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摘 要

目的：都卜勒超音波可用於偵測各種腎臟病，例如移植腎排斥，尿路阻塞，腎動脈高血壓和腎實質性病變，本篇研究目的在1.評估都卜勒超音波測出的阻抗力指標（RI）和腎切片結果的關係。2.決定RI值能否預測狼瘡性腎炎的療效。44位初次被診斷的狼瘡性腎炎被納入研究。

方法：作腎切片前，執行都卜勒超音波。治療6個月後，分析治療成效。

結果：發現1.腎切片的慢性化指標（CI）在高RI的21位病人也是高的，相較於正常RI的病人。2. 22位治療沒有反應的病人，他們的RI值是較高的。3.在回歸模式，高RI值是和較差的治療反應有關。

結論：都卜勒超音波的RI值與腎切片的CI值有良好相關，而且可以預測治療反應。

關鍵字：狼瘡，阻抗力指標，慢性化指標

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