Original Paper

Assessment of Renal Pathological Changes in Lupus Nephritis Using Diffusion Weighted Imaging: A Multiple Correspondence Analysis

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Key Words

Lupus nephritis • Diffusion weighted imaging • Renal pathology • Multiple correspondence analysis • Magnetic resonance imaging

Abstract

Background/Aims: Renal pathological changes affect the motion of water molecules, which can be detected using diffusion-weighted imaging (DWI). The current study was performed to explore the correlation between renal tissue pathological injuries and DWI iconographical parameters in lupus nephritis (LN). **Methods:** Twenty adult patients with LN and 11 healthy volunteers were recruited. Patients with LN received renal biopsies and renal DWI-MRI inspections. The renal biopsy tissues were characterized based on the ISN/RPS 2003 classification. The volunteers, who were of comparable gender and age, only underwent renal DWI-MRI inspection. Four DWI parameters, namely, apparent diffusion coefficient (ADC), pure diffusion coefficient (D_t), pseudo-diffusion coefficient (D_p), and perfusion fraction (f_p), were calculated using monoexponential and biexponential functions, respectively. Data from different renal areas and pathological pattern groups were compared. Multiple correspondence analysis (MCA) was performed to explore the correlation between each DWI index and multiple pathological features. **Results:** ADC, D_t , and f_p values were lower in the LN group compared to the controls ($P < 0.001$) regardless of the renal area in the cortex and medulla. D_p values were higher in the LN group ($P = 0.004$). A difference in mean DWI parameters was found between three LN subgroups and the healthy volunteers, with the exception of the D_p index in the renal cortex. MCA showed that serious proliferative pathological injuries and lower ADC and D_t values were located in the same quadrant. The MCA plots of D_p and f_p provided similar results. Higher D_p and f_p values were located in the MCA plot quadrant with more serious

proliferative pathological changes. **Conclusion:** DWI is a noninvasive technique that may be used to detect renal pathophysiological changes. Renal cell proliferation and intestinal fibrosis may impact the movement of water in certain microenvironments. Enhanced perfusion may be a compensatory mechanism that is associated with renal pathological injuries.

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Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with diverse clinical manifestations, and multiple environmental and/or genetic pathogenesises [1]. The renal system is commonly involved in patients with SLE and it is also a significant cause of morbidity and mortality [2]. Lupus nephritis (LN) is one of the most common forms of secondary glomerulonephritis in China. An epidemiological investigation by Pan et al., reported that LN was found in approximately 2.37% to 25% of all biopsy-confirmed renal diseases and in approximately 27.2% to 80.65% of renal disease biopsies performed for secondary causes of glomerular disease [3]. Clinically, renal biopsy is a useful assessment method in patients with LN. However, due to the increased risk of complications, such as bleeding, its use is limited. Therefore, the identification of a noninvasive, real-time method of assessing renal structure and function is needed.

Functional MRI techniques, such as diffusion-weighted imaging (DWI), have the potential to assess intra-renal pathophysiological changes and abnormal kidney function. For example, previous studies have shown a close correlation between renal tissue microstructure and the apparent diffusion coefficient (ADC), which is calculated from DWI signals with monoexponential functions. Furthermore, considering the microenvironment intravoxel incoherent motion (IVIM) effect, and calculating other parameters via biexponential function, allows for the assessment of pure molecular diffusion separate from microcirculation (capillary diffusion). The IVIM model provides multiple significant DWI-MRI indices, including true-diffusivity (D), pseudo-diffusivity (D_p), and perfusion fraction (f_p) [4-6]. Reduced ADC values have been detected in patients with renal dysfunction and attributed to either reduced water reabsorption or renal fibrosis, which restricts water diffusion [7, 8]. Thus, IVIM analysis has the potential to assess different aspects of renal physiology, such as vascular perfusion, tubular flow, and water reabsorption [4]. Clinically, radiologists and nephrologists appreciate the utility of the DWI-MRI technique in assessing renal physiological or pathological changes. Previous studies have shown that the DWI technique is a sensitive method for detecting renal function in patients with chronic kidney disease [9], evaluating renal allografts function [10], assessing the severity of renal pathology, and guiding therapy for patients with CKD [11]. To the best of our knowledge, only two studies focused on the use of DWI-MRI in LN have been published. One study, published by Rapacchi et al. in 2015, evaluated 10 LN patients and 10 matched healthy volunteers. In this study, the ADC values determined by DWI-MRI were not significantly different between the LN and control groups [12]. Another study by Li et al. (2014), which recruited 65 LN patients and 16 healthy volunteers, found a negative correlation between the mean ADC values and renal pathology chronicity indices [13]. Due to the limitations of using monoexponential function algorithmic ADC values, these two studies failed to uncover detailed pathological information.

The primary purpose of this study was to investigate the correlation between DWI-MRI iconographical features and renal pathological characteristics. We used a biexponential formula algorithm in addition to other DWI parameters to investigate multiple pathological injuries that impact the motion of water molecules in the renal tissue microenvironment of patients with LN.

Materials and Methods

Study Protocol

Participants. This single-center observational study was approved by the Ethics Committee of Tianjin Medical University General Hospital, and informed consent was obtained from all of the participants. This study was conducted in accordance with the Declaration of Helsinki. Twenty patients and 11 healthy volunteers were recruited from January 2015 to June 2017. All of the patients fulfilled the 2012 International Collaborating Clinics classification criteria and all of them had undergone renal biopsy [14]. Disease activity was assessed using the SLEDAI (SLE Disease Activity Index) [15], and serum creatinine values were used to calculate current estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [16]. Healthy volunteers were recruited from different divisions of the hospital; no evidence of kidney disease or renal injury was found among these participants. Twenty recruited patients with LN received underwent renal biopsy and DWI-MRI inspection. Eleven healthy volunteers of comparable gender and age only underwent DWI-MRI inspection. To eliminate the effects of medication on results, all of the patients and healthy volunteers were not allowed to use angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), diuretics, or vasodilators for at least two weeks, as these agents may impact renal blood flow and tubular liquid transportation.

Renal Histopathology. Renal biopsy specimens were fixed in 4.5% buffered formaldehyde for analysis via light microscopy. Consecutive serial 2-um sections were used for histological staining. Stains used included hematoxylin and eosin, periodic acid-Schiff, silver methenamine, and Masson's trichrome. The renal histopathological data from 20 patients with renal biopsy-confirmed LN were diagnosed by two experienced pathologists according to the ISN/RPS 2003 classification [17]. The pathologists classified and scored the biopsies separately and they were blinded to the patient data and the scores of the other observers. Patients with less than 10 glomeruli in their renal biopsies were excluded. For this study, cases of III+V were classified as class III and cases of IV+V were classified as class IV. Pathological parameters, such as activity indices and chronicity indices, were approximated by renal pathologists using a modified, previously reported system involving semi-quantitative scoring of specific biopsy features [18].

Magnetic Resonance Imaging Techniques. Magnetic resonance imaging was performed using a 3.0-T Imager (GE Discovery 750 3.0T, General Electric, USA). The scanner had a maximum gradient strength of 50 mT/m and a slew rate of 200 mT/m/sec. A Torsopa eight-channel body coil was used. Images were acquired for morphologic evaluation using a T_1 -weighted fat-suppressed sequence. Images were acquired with a T_1 INPHASE+FAT sequence. The field of view (FOV) was 380×380 mm, the section thickness was 7.0 mm, the section width was 1.0 mm, and repetition time (TR)/echo time (TE) was 4286/62.5. Multi b-value DWI-MRI was performed using single-shot echo planar imaging (EPI). Duplicate T_1 WI scans were performed at baseline. Images were acquired with 10 b-values (0, 50, 100, 150, 200, 250, 300, 500, 800, and 100 s/mm²) to sample both the IVIM pseudo-diffusion decay ($b < 200$ s/mm²) and the molecular diffusion decay ($b > 200$ s/mm²). Parameters of DWI are including 8 section number and 8 minutes in each scan time.

Image Analysis. DWI parameter maps, including ADC, D_v , D_p , and f_p were constructed on an ADW 4.5 Workstation using the Functool program. Four renal coronal index planes were selected from bilateral kidneys in each participant, so we acquired four groups of DWI images (ADC, D_v , D_p , and f_p), with each group including four images (two images of the left kidney and two images of the right kidney). In each coronal DWI parameter plane, the region of interest (ROI) were manually defined in the cortex and medulla. DWI parameter values of each voxel of the selected ROI were obtained by MATLAB 7.10 (MathWorks Inc., Natick, MA, USA). Patient DWI parameter values were calculated using the arithmetic mean of the ROIs in four DWI parameter planes.

The ADC value was calculated using mono-exponential function. The relationship between signal variation and b factors was expressed using the following equation:

$$S_b/S_0 = e^{-bADC}$$

The IVIM model considers the diffusivity (D) of the tissue and signal attenuation due to flowing spins. In the kidney, the signal from the flowing spins depends upon the capillary or tubular geometry and the flow velocity. The relationship between the signal variation and b factors was expressed using the following equation:

$$S_b/S_0 = (1 - f_p)e^{-bD_t} + f_p e^{-bD_p}$$

where b represents the strength of the diffusion gradient, S_0 the signal intensity without a diffusion gradient, S_b is the signal intensity at a given b value, f_p is the fraction of diffusion linked to microcirculation, D_t is the tissue diffusivity representing pure molecular diffusion, and D_p is the diffusion parameter representing blood or tubular flow.

Statistical Analyses

Multivariate Analysis. To compare the difference in the DWI parameters between groups, we used the multivariate analysis of variance (MANOVA) model. MANOVA provides an omnibus test of statistical significance. If this test was statistically significant for the key independent variable, then post hoc comparisons were run to identify which group was statistically different. There are four MANOVA output statistics (Wilk's Lambda, Lawley-Hotelling trace, Pillai's trace, and Roy's largest root) that may be used to judge whether differences between groups exist.

Multiple Correspondence Analysis.

To analyse the relationship between DWI parameters and renal pathological parameters, multiple correspondence analysis (MCA) was applied. MCA is a descriptive/exploratory technique designed to analyze simple two-way and multi-way tables containing measures of correspondence between the rows and columns. The object of MCA is to visualize the relationship of categorical parameters in a graphical manner. Correspondence analysis was used to explore the relationship between variables by comparison with distance in multiple dimension space. In general, the first two dimensions can usually explain the majority variation. We used two dimensions to visualize the correlation of the variables. Detailed, categorized information on DWI indices and pathological parameters are illustrated in Table 1.

Table 1. Value assignment of clinical and pathological indices in lupus nephritis

Indexes description	Scale category	Value assignment
Glomerular cell proliferation	None	1
	Less than 25%	2
	25% to 50%	3
	Greater than 50%	4
Leucocyte exudation	None	1
	Mild	2
	Moderate	3
	Extensive	4
Karyorrhexis and fibrinoid necrosis	None	1
	Less than 25%	2
	25% to 50%	3
	Greater than 50%	4
Cellular crescents	None	1
	Less than 25%	2
	25% to 50%	3
	Greater than 50%	4
Hyaline deposits	None	1
	Mild	2
	Moderate	3
	Extensive	4
Interstitial inflammation	None	1
	Mild	2
	Moderate	3
	Extensive	4
Glomerular sclerosis	None	1
	Less than 25%	2
	25% to 50%	3
	Greater than 50%	4
Fibrous crescents	None	1
	Less than 25%	2
	25% to 50%	3
	Greater than 50%	4
Tubular atrophy	None	1
	Mild	2
	Moderate	3
	Extensive	4
Interstitial fibrosis	None	1
	Mild	2
	Moderate	3
	Extensive	4
Thicken basement membranes	No	1
	Yes	2
ADC value	Less than Q1	1
	Q1~Q2	2
	Q2~Q3	3
	Greater than Q3	4
D_t value	Less than Q1	1
	Q1~Q2	2
	Q2~Q3	3
	Greater than Q3	4
D_p value	Less than Q1	1
	Q1~Q2	2
	Q2~Q3	3
	Greater than Q3	4
f_p value	Less than Q1	1
	Q1~Q2	2
	Q2~Q3	3
	Greater than Q3	4

All of the analyses were carried out using IBM®SPSS® Statistics software (version 22.0 IBM Corporation; Armonk, NY, USA). Data in the text and table are shown as mean $\pm$ SD. Statistical significance was determined at $P < 0.05$.

Results

Participant Demographic Information

There were 20 patients in the LN group who were included in the study and underwent DWI-MRI. The average age of the patients was 34.30 ± 14.31 years (ranging from 16–62 years). The mean urine protein was 3.71 ± 2.81 g/24 h (ranging from 0.34–9.47 g/24 h) and the mean eGFR was 100.60 ± 25.45 ml/min/1.73 m² (ranging from 39–138 ml/min/1.73 m²). In the LN group, the mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 140.00 ± 14.86 mmHg and 83.05 ± 8.08 mmHg, respectively. All 20 of the patients underwent a renal biopsy. According to the 2003 ISN/RPS classification system for LN, renal pathological patterns were listed as: III-(A/C) pattern (2 cases), III-(A/C) + V pattern (3 cases), IV-G(A/C) pattern (3 cases), IV-S(A/C) pattern (1 case), IV-S(A) pattern (1 case), IV-G(A/C) + V pattern (5 cases), IV-S(A/C) + V pattern (1 case), and V pattern (4 cases). Eleven individuals were recruited for the healthy volunteer group and they underwent DWI-MRI. The average age of the healthy volunteers was 33.73 ± 13.59 years (ranging from 16–56 years). The mean eGFR of the healthy volunteers was 117.00 ± 13.19 ml/min/1.73 m² (ranging from 99–141 ml/min/1.73 m²). The mean SBP and DBP in the healthy volunteers were 132.18 ± 8.10 mmHg and 81.73 ± 6.81 mmHg, respectively. No statistically significant difference in age or eGFR was found between the LN group and the healthy volunteers.

Comparison of Renal DWI-MRI Values between LN Patients and Healthy Volunteers

The mean ADC, D_t , and f_p values were lower in the LN patients than in the healthy volunteers ($P < 0.001$ for all of the parameters) regardless of the renal area in both the cortex and medulla. However, the opposite results were found for D_p ($P = 0.004$). Details are provided in Table 2 and Fig. 1.

In the renal cortex area, differences in mean DWI parameters were found between the three LN subgroups and the healthy volunteers group, except for the mean D_p index. Details are provided in Table 3 and Fig. 2. Similar results were also found in the renal medulla area; details are provided in Table 4 and Fig. 3.

Multiple Correspondence Analysis of DWI-MRI Parameters and Pathological Indices

We explored the complex interrelationships between the pathological indices and DWI-MRI parameters. In the MCA figure between ADC and renal pathological indices, the lower ADC values and several graded pathological characteristics were located in the lower right quadrant. These pathological characteristics included glomerular sclerosis, cellular crescents, glomerular cell proliferation, and interstitial fibrosis; details are provided in Fig. 4. These renal pathological injuries may decrease the capacity of molecular diffusion in renal tissues. Similar results were also found in the MCA figure between D_t and renal pathological indices; details are provided in Fig. 5.

Table 2. Comparison of DWI functions between groups with lupus nephritis and healthy volunteers. Note: ADC: appearance diffusion coefficient; D_t : true diffusion coefficient; D_p : pseudo-diffusion coefficient; and f_p : perfusion fraction. Data are shown as mean $\pm$ SD

DWI functions	Renal cortex			Renal medulla		
	Lupus nephritis (N = 20)	Healthy volunteers (N = 11)	P value	Lupus nephritis (N = 20)	Healthy volunteers (N = 11)	P value
ADC	2.284 ± 0.184	2.393 ± 0.085	< 0.001	2.258 ± 0.174	2.358 ± 0.067	< 0.001
D_t	1.677 ± 0.314	1.802 ± 0.285	< 0.001	1.597 ± 0.348	1.734 ± 0.272	< 0.001
D_p	22.391 ± 1.979	22.003 ± 2.033	0.004	23.079 ± 1.333	22.528 ± 1.633	0.004
f_p	22.343 ± 2.033	23.949 ± 0.321	< 0.001	22.368 ± 1.581	23.530 ± 0.735	< 0.001

Fig. 1. Comparison of DWI indices between lupus nephritis patients and healthy volunteers.

Table 3. Comparison of DWI functions in the renal cortex between lupus nephritis subgroups and healthy volunteers. Note: ADC: appearance diffusion coefficient; D_t : true diffusion coefficient; D_p : pseudo-diffusion coefficient; and f_p : perfusion fraction. Data are shown as mean $\pm$ SD

DWI functions	Lupus nephritis III class (N = 5)	Lupus nephritis IV class (N = 11)	Lupus nephritis V class (N = 4)	Healthy volunteers (N = 11)	P value
ADC	2.217 $\pm$ 0.219	2.303 $\pm$ 0.122	2.358 $\pm$ 0.120	2.393 $\pm$ 0.085	< 0.001
D_t	1.548 $\pm$ 0.304	1.688 $\pm$ 0.302	1.781 $\pm$ 0.305	1.802 $\pm$ 0.285	< 0.001
D_p	22.768 $\pm$ 1.326	22.535 $\pm$ 2.132	21.703 $\pm$ 2.317	22.003 $\pm$ 2.033	0.059
f_p	22.167 $\pm$ 2.191	22.286 $\pm$ 1.745	23.188 $\pm$ 1.062	23.949 $\pm$ 0.321	< 0.001

Fig. 2. Comparison of renal cortical DWI indices among three subclasses of lupus nephritis and healthy volunteers.

Table 4. Comparison of DWI functions in the renal medulla between lupus nephritis subgroups and healthy volunteers. Note: ADC: appearance diffusion coefficient; D_t : true diffusion coefficient; D_p : pseudo-diffusion coefficient; and f_p : perfusion fraction. Data are shown as mean $\pm$ SD

DWI functions	Lupus nephritis III class (N = 5)	Lupus nephritis IV class (N = 11)	Lupus nephritis V class (N = 4)	Healthy volunteers (N = 11)	P value
ADC	2.212 $\pm$ 0.176	2.276 $\pm$ 0.136	2.302 $\pm$ 0.172	2.358 $\pm$ 0.067	< 0.001
D_t	1.422 $\pm$ 0.224	1.660 $\pm$ 0.310	1.668 $\pm$ 0.423	1.735 $\pm$ 0.272	< 0.001
D_p	23.179 $\pm$ 1.136	23.237 $\pm$ 1.157	22.761 $\pm$ 1.835	22.528 $\pm$ 1.633	0.019
f_p	22.118 $\pm$ 1.761	22.712 $\pm$ 1.088	22.575 $\pm$ 0.939	23.530 $\pm$ 0.735	< 0.001

Fig. 3. Comparison of renal medullary DWI indices among three subclasses of lupus nephritis and healthy volunteers.

Fig. 4. Multiple correspondence analysis of ADC and renal pathological parameters in 20 lupus nephritis patients.

In the MCA figure showing the relationship between D_p and renal pathological indices, the higher D_p values and several pathological injuries, such as cellular crescents, glomerular cell proliferation, interstitial fibrosis, hyaline deposits, and tubular atrophy, were scattered in the same quadrant; details are provided in Fig. 6. Similar results were also found in the MCA figure showing the relationship between f_p values and renal pathological indices. These results demonstrate the close correlation between renal pathological injuries and fluid perfusion; details are provided in Fig. 7.

Fig. 5. Multiple correspondence analysis of D_t and renal pathological parameters in 20 lupus nephritis patients.

Fig. 6. Multiple correspondence analysis of D_p and renal pathological parameters in 20 lupus nephritis patients.

Fig. 7. Multiple correspondence analysis of f_p and renal pathological parameters in 20 lupus nephritis patients.

Discussion

The current study investigated the discrepancy between diffusion and tissue perfusion in patients with LN and healthy volunteers. The DWI-MRI results implied that decreased diffusion and incremental fluid perfusion co-existed in renal tissues in patients with LN. We speculated that these abnormal manifestations of intra-renal fluid movement might correlate with pathophysiological changes in LN. Previous studies have shown that multiple pathological injuries are found in both the glomerular and tubule-interstitial areas. The injuries included the proliferation of endothelial and mesangial cells, proliferation of parietal epithelial cells, crescent formation, tubular atrophy, and interstitial fibrosis [19]. These pathological injuries may weaken the capacity for the free diffusion of fluid, which has been observed by DWI-MRI. For example, Li et al. compared renal ADC values between 65 LN patients and 16 healthy volunteers and they found that the mean ADC values of the kidneys in LN patients were significantly lower than in the healthy volunteers regardless of both the renal cortex and renal medulla area [13]. Although the precise mechanism behind the decline of ADC and D_t has not been determined, it may be due to higher cell density. Increased tissue cell density can lead to fluid redistribution in the tissue microenvironment. For example, Chin et al. found that high cell density decreased the extracellular water fraction and increased the intracellular water fraction, resulting in a lower ADC [20]. In contrast, our study results showed an increase in perfusion in both the renal cortex and renal medulla. This may be due to renal pathological injuries that give rise to neovascularization in patients with LN. In a study by Frieri et al., vascular endothelial growth factor (VEGF) expression in the renal tissues of eight LN patients was compared with a healthy control group. Their results showed a significant increase in VEGF expression in the LN group [21]. Similarly, Ding et al. measured VEGF levels in 41 LN patients and found higher blood and urinary VEGF levels in the LN group [22]. Therefore, increased VEGF levels may promote the microvascular proliferation and increased water molecular perfusion detected by DWI-MRI.

In the current study, we also compared the DWI parameters of the renal cortex and medulla in both the LN and healthy volunteer groups. In the healthy volunteer group, there was a difference in two of the DWI parameters (ADC and f_p) between the cortex and

medulla. However, the DWI parameters, D_t and D_p , which represent molecular diffusion and perfusion, respectively, were not significantly different between the renal cortex and the medulla. Therefore, we speculate that diffusion and perfusion in the renal cortex and medulla is similar under normal physiological conditions in a healthy population. To maintain an optimal glomerular filtration rate and cortical-medullary solute gradient, most blood is directed towards the renal cortex, where approximately 10% of the renal blood supply is dedicated to medullary afflux [23]. Since the PF value represents the proportion of the DWI-MRI signal that is perfusion, the higher PF value in the cortex may reveal this renal physiological characteristic in our current study. One interesting result of the current study was the contradictory data showing differential values of ADC and D_t between the cortex and medulla. Although these two DWI parameters are thought to be indices of diffusion, there were still slight distinctions between the two parameters. In contrast with how the ADC was calculated, D_t was calculated using the biexponential formula with consideration of the effect of intravoxel incoherent motion (IVIM) [6]. The IVIM effect might be mistaken as a diffusion effect when using the monoexponential formula, which was utilized to calculate the ADC parameter. In patients from the LN group, a difference in two parameters (D_t and D_p) between the renal cortex and medulla were observed. Compared with the same index in the healthy volunteer group, the D_t values were lower in both the cortical and medullary tissues. Since D_t values in the medullary area declined significantly, the cortical-medullary statistical distinction of this index was detected by DWI. We presume that diffusion in the renal medulla was affected by various pathological changes in patients with LN. Unfortunately, there was not enough renal pathological evidence to test this theory because there is a high risk of bleeding during a medullary tissue biopsy. However, based on renal cortical-medullary tissue and cellular structure and physiological functional discrepancies, we could detect the more serious renal parenchymal fibrosis located in the medullary area. Previous studies have shown a correlation between decreased ADC and the magnitude of fibrosis [24, 25]. However, other studies have shown the opposite effect with D_p . The fluid perfusion capacity in the microenvironment of patients with LN was significantly reinforced, particularly in the renal medulla. We hypothesized that the enhanced fluid perfusion effect in the renal parenchyma could be a compensatory pathophysiological mechanism by which the tissue may compensate for the diminishing diffusion effect in the tissue microenvironment. Although an explanation for the higher perfusion effect detected in the renal medulla is unknown, previous studies may provide a potential mechanism. For example, studies have shown that intra-renal nitric oxide (NO) levels increase in patients with LN compared with healthy controls. NO is produced by a family of NO synthases (NOS), of which three major isoforms exist, namely, neuronal (nNOS), inducible (iNOS), and endothelial (eNOS) NOS, which have been detected in the renal parenchyma [26, 27]. Furthermore, nNOS is predominantly present in the macula densa; iNOS is located in the medullary thick ascending limb and collecting ducts; and eNOS is scattered in the glomerular capillaries, intra-renal arteries and arterioles, vasa recta, proximal tubules, and thick ascending limbs [28, 29]. Previous studies have shown higher NOS activity in the medulla compared to the cortex [30].

D_t and D_p represented the water molecule free diffusion capability and microenvironment perfusion capability, respectively. We speculated that there was a similar renal cellular and tissue physiological condition in the both cortex and medulla in healthy volunteers. However, significant differences of these two DWI parameters were detected between the cortex and medulla in the LN group. These results might indicate that LN pathophysiological injuries have an impact on different effects in the renal cortex and renal medulla. Although some previous studies showed the close correlation between ADC value and eGFR, we did not think that these DWI parameters were used to measure the glomerular function. The DWI-MRI technique was used to detect water molecule and fluid movement rather than glomerular blood flow.

We also explored the correlation between the eGFR and DWI parameters. Unfortunately, no substantial correlative findings were detected on the basis of our research data.

We speculated several possible reasons might lead to our current results. First, renal pathophysiological injuries of LN were sophisticated. Different pathological patterns or injury degree might impact eGFR in complicated ways. The higher pathological heterogeneity perhaps disturbed the correlation of the DWI parameters and eGFR. Second, the clinical index of eGFR implied the renal eliminating fluid capacity. However, the DWI parameters, such as D_t and D_p , represented water molecule free diffusion capacity and microenvironment fluid perfusion capability. There were still substantial differences when detecting renal pathophysiological status. Third, our study only included 20 LN patients. We did not exclude the possibility of sample error. Based on these reasons, we did not recommend using these DWI indexes to measure the glomerular function.

The current study also investigated the characteristics of diffusion and perfusion among the different pathological patterns of LN. Surprisingly, we found that the lowest renal diffusion levels were detected in patients with Class III LN instead of Class IV LN. It is well recognized that the pathological injuries in Class IV are more serious than in Class III. However, our results did not show a difference in diffusion between Class III and Class IV in both the cortex and medulla. Moreover, we found lower diffusion in the Class III group instead of the Class IV group when compared to the Class V and healthy volunteer groups. These results suggest that the relationship between renal pathological changes is complex, as is their impact on diffusion.

In addition, we assessed the difference in perfusion levels in three pattern LN groups and the healthy volunteer group. Interestingly, two perfusion indices, D_p and f_p , showed opposite results. We did not find obvious changes in D_p levels among the different groups, except for the Class IV LN group D_p values in the medulla. In contrast, the PF index in all three of the pattern LN groups showed lower values when compared with the healthy volunteer group in both the cortical and medullary areas. Since D_p denotes perfusion, and f_p represents the proportion of tissue perfusion, we hypothesized that the perfusion effect was not significantly enhanced in patients with LN, particularly in the cortical area. However, the proportion of perfusion in the renal tissue microenvironment was significantly decreased in comparison with healthy volunteers, especially in the Class IV group, which had more serious pathological injuries. We therefore speculated that the f_p values may correlate with the extent of tubular atrophy and microvascular thrombosis.

To explore the correlation between changes in diffusion and perfusion and multiple pathological injuries, a multivariate technique (MCA) was used to visualize this relationship within a set of categorical variables. In the MCA plot of D_t and pathological injuries, the lowest D_t (less than Q1) was located in the lower right quadrant. Cellular crescents, glomerular cell proliferation, interstitial fibrosis, and leucocyte exudation in the absence of thickened basement membranes were also distributed in the same area. These results imply that renal cell and extracellular matrix proliferation, inflammatory cell infiltration, and interstitial fibrosis may be major factors that impact water diffusion. In the MCA plot of D_p and pathological injuries, the highest D_p (greater than Q3) was located in the upper left quadrant. Similar pathological pattern injuries were also scattered in the same quadrant. It appeared that serious proliferative pathological changes may be concomitant with enhanced tissue microenvironment perfusion. Therefore, we hypothesized that this variation is one mechanism of renal compensation.

There were several limitations in the current study. First, the study had a small sample size of 20 LN patients and 11 healthy volunteers. The sample was too small to gain a robust result. Moreover, other pathological classes and subclasses, such as class II, III-C, III-A, IV-G(C), IV-S(A) or VI, were not included in this study. Second, other factors, such as blood pressure and water or liquid intake, which could potentially impact DWI parameters, were not analyzed. Third, although the MCA plots provided a visual correlation between the DWI parameters and pathological injury patterns, the MCA technique is a statistical exploration technique instead of a statistical test, which would provide robust results. Fourth, our current study did not analyze the correlation between volume status and DWI parameters.

Several impersonal reasons give rise to the failure to assess the participants' volume status accurately. For example, our hospital provided several static and dynamic volume status techniques. However, these techniques were all invasive and all of participants refused these medial inspections. Noninvasive assessing techniques, such as bioelectrical impedance analysis (BIA) or noninvasive cardiac output monitor (NiCOM), were not available in our study. Therefore, future studies are needed to definitively show the relationship between the DWI parameters and renal pathological indices in patients with LN.

Conclusion

DWI-MRI is a useful non-invasive technique for detecting renal pathophysiological changes. Pathological injuries in patients with LN may decrease diffusion, while renal cell proliferation and intestinal fibrosis may impact the free movement of fluids in tissue microenvironments. Enhanced perfusion is a potential compensatory mechanism associated with renal pathological injuries. DWI parameters may be linked with multiple pathological indices; however, the relationship is complex.

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Disclosure Statement

The authors declare that they have no competing interests.

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