Functional evaluation of secondary renal amyloidosis with diffusion-weighted MR imaging

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ABSTRACT

Objectives This study evaluated whether diffusion-weighted magnetic resonance imaging (DW-MRI) can be used to diagnose secondary renal amyloidosis looking specifically at the diagnostic efficacy of two apparent diffusion coefficient (ADC) measurement methods as they were used with DW-MRI. Methods The study included 24 amyloid nephropathy (AN) patients, 20 chronic kidney disease (CKD) patients, and 20 healthy volunteers (HV). ADC values were measured using two different methods: 1) the method of the region of interest indicators (ROIs) and 2) the method of drawing whole renal parenchyma (WP). The correlation between the two methods was evaluated. Results ROIs could differentiate AN-CKD \((p = 0.007)\). ROIs and WP could differentiate AN-HV \((p < 0.05)\). However, none of the methods could differentiate CKD-HV \((p > 0.05)\). The sensitivity and specificity of the ROIs method in differentiating AN from CKD patients for \(1.8 \times 10^{-3}\) cutoff ADC values were 79% and 60% and for AN-HV patients 79% and 70%. ADC values of AN patients with GFR > 60 mL/min were lower than that of HV \((p < 0.01)\). Conclusion DW-MRI is a useful and non-invasive diagnostic tool in diagnosing secondary renal amyloidosis and differentiating renal amyloidosis from other CKDs. ROIs had the highest sensitivity and specificity for assessing the involvement of renal amyloidosis. MRI diagnosis of AN may obviate a renal biopsy for diagnosis.

Introduction

Amyloidosis is a disease in which organ dysfunction occurs as a result of deposition of protein in the form of insoluble fibrils in the extracellular area of tissues.\(^1\) Secondary amyloidosis can arise as a complication of any kind of chronic inflammatory, infectious, and neoplastic diseases such as rheumatoid arthritis, familial Mediterranean fever (FMF), or inflammatory bowel disease. Renal involvement is a cause of major morbidity for patients having amyloidosis.\(^5\)–\(^9\)

Renal involvement is seen in 80% of secondary amyloidosis patients.\(^1\)–\(^4,10\) It is usually manifested as proteinuria in 95% or nephrotic syndrome in 50% of patients. Glomerular deposition is common and is associated with a poor renal outcome. Eighty-five percent of individuals in this category show progression to end-stage renal disease during a 2–13-year follow-up period. Nonetheless, when vascular and tubular amyloid deposits are present their prognosis is usually more favorable with a more slowly progressive chronic kidney disease (CKD).\(^11\)

Amyloidosis is diagnosed by the detection of amyloid deposits histologically on samples taken from gingiva, rectum, salivary gland, renal biopsy, and abdominal fat sampling.\(^5\) The aim with amyloid deposition should be an early diagnosis, if possible without a biopsy. Early diagnosis and anti-inflammatory therapy provide regression of amyloid deposits and, recovery of the organ function. Thereby excellent long-term survival may be provided.\(^10,12\) Apart from renal tumors\(^15\)–\(^17\), studies were done using diffusion-weighted magnetic resonance imaging (DW-MRI) on diffuse renal diseases such as ureteral obstruction,\(^18\) renal artery stenosis,\(^19\)–\(^21\) hydronephrosis, pyelonephritis,\(^22,23\) and CKD.\(^21,23–25\) It is reported that the diffusion is restricted in these diseases and the apparent diffusion coefficient (ADC) values are significantly different from those of the healthy people.

Karadeli et al.\(^26\) evaluated the feasibility of DW-MRI in the assessment of renal function in 60 patients with FMF. They concluded that DW-MRI of the kidneys might allow early detection of renal changes in patients with FMF. On the other hand, when the relevant literature is evaluated, research showing whether renal amyloidosis and chronic renal failure can be differentiated by DW-MRI has not been found.

In this study, ADC values were measured in DW-MRI in healthy volunteers (HV), CKD patients, and secondary
inhibitors (ACE), one patient was receiving angiotensin II receptor blockers (ARB). One patient was receiving calcium channel blockers (CCB). One patient was receiving furosemide. Six of the patients with CKD were receiving CCB and beta blocker (BB). Two patients were receiving CCB and ARB. One patient was receiving CCB and alpha one adrenergic receptor blocker. Two patients were receiving CCB and thiazide. Three patients were receiving ARB. Two patients were receiving ACE. Two patients were receiving ARB and thiazide. Two patients were receiving BB.

The staging of patients in AN and CKD groups was done with respect to the kidney disease outcome quality initiative criteria as shown in Table 1. Moreover, the disease stages of the patients included in the study are summarized in Table 2.

### MR imaging

The study was carried out with 1.5-T MRI (Optima 450W, General Electric Medical Systems, Milwaukee, WI). The patients were examined in the supine position with a 12 channeled body coil. Using respiratory triggering technique, the examination was conducted on a coronal plane with Propeller T2 DW sequences with and without fat saturation. The imaging parameters of T2-weighted images were set as follows: slice thickness 5 mm, interslice gap 1 mm, field of view (FOV) 400 × 400, matrix size 288 × 288, TE 82.1 ms, TR 4000 ms, and flip angle 160°. In DW examination, the b value was chosen as 1000 s/mm². The gradients were applied in three orthogonal directions and subsequently averaged to minimize the effects of diffusion anisotropy. The imaging parameters were set as follows: FOV 380 × 380, slice thickness 5 mm, interslice gap 1 mm, matrix 256 × 256, bandwidth 250 kHz and NEX 4.

### Image analysis

Image analyses were done on the workstation (GE Advantage Workstation AW4.2_08) using Functool 2 image analysis software (GE Medical Systems).

### Morphological evaluation

The morphological evaluation was made by two radiologists who were experienced and blind to the DW-MRI images. The
presence of parenchymal lesions together with their sizes, parenchymal signal intensity change, and collecting duct system dilatation were examined respectively.

**ADC calculation techniques**

ADC measurements were performed on mesorenal areas as in some previous studies. The image resolution was not sufficient to differentiate the cortex and the medulla since the diffusion images were captured at a high $b$ value. Thus, region of interest (ROI) indicators were placed on the corticomedullar junction. Two methods were used in the measurements. In the first method, measurements were taken from upper pole, middle zone, and lower pole by placing circular ROI indicators. The first ROI indicator used was copied and examination continued. All ROI placements were done by an experienced radiologist in abdominal MRI. For all cases, three measurements were taken from two kidneys. Then, the average of all measurements was calculated and a single ADC value was obtained for all patients as shown in Figure 1. In the second method, all renal parenchyma was drawn by hand once again and average ADC values were measured as shown in Figure 2. Cysts were excluded from measurements. Measurements were performed individually on images with fat saturation, and the results of both methods were compared.

**Statistical analysis**

The data analysis was done using SPSS for Windows 15 software (SPSS Inc., Chicago, IL). Mean ± standard deviation was presented for the variables with normal distribution, and median (minimum – maximum) was presented for variables without normal distribution. Furthermore, a number of cases and percentages (%) were presented for nominal variables. When the number of groups is two, the significance of the mean difference among the groups was investigated using $t$-test whereas the significance of the median difference among the groups was investigated using Mann–Whitney $U$ test. When the number of groups is greater than two, the significance of mean difference among the groups was investigated using ANOVA variance analysis test whereas the significance of difference among the groups with regard to median values was investigated using Kruskal–Wallis test.

The nominal variables were evaluated using Pearson $\chi^2$ or Fisher’s Exact test. The interclass correlation coefficient and its significance were investigated for the correlation between two continuous variables. Spearman correlation test was used when the distribution was not normal during the investigation of the relationship between continuous variables, whereas...
Table 3. The mean and median (min-max) ADC values according to the measurement methods.

| Measure method | Cutoff ADC-value | Sensitivity (95% CI) | Specificity (95% CI) |
|---------------|------------------|----------------------|----------------------|
| ROIs (n=14)   | 1.8 x 10^-3      | 79 (58-93)           | 70 (46-88)           |
| WP (n=10)     | 1.9 x 10^-3      | 83 (63-95)           | 65 (41-85)           |

Table 4. Analysis of the ROC curve of an-HV comparison.

| Measure method | Cutoff ADC-value | Sensitivity (95% CI) | Specificity (95% CI) |
|---------------|------------------|----------------------|----------------------|
| ROIs (n=14)   | 1.8 x 10^-3      | 79 (58-93)           | 60 (36-81)           |
| WP (n=10)     | 1.7 x 10^-3      | 33 (16-55)           | 95 (75-99)           |

Table 5. Analysis of ROC curve of an-CKD comparison.

| Group          | Measure method | Cutoff ADC-value | Sensitivity (95% CI) | Specificity (95% CI) |
|----------------|----------------|------------------|----------------------|----------------------|
| HV (n=20)      | ROIs           | 1.9 ± 0.13 x 10^-3 | 60 (58-93)           | 95 (75-99)           |
| AN-GFR > 60    | ROIs           | 1.8 ± 0.10 x 10^-3 | 60 (58-93)           | 95 (75-99)           |
| AN-GFR > 60    | WP             | 0.003             |                      |                      |

Table 6. Comparison of HV-AN with GFR > 60 mL/min.

| Group          | Measure method | Cutoff ADC-value | Sensitivity (95% CI) | Specificity (95% CI) |
|----------------|----------------|------------------|----------------------|----------------------|
| HV (n=20)      | ROIs           | 1.9 ± 0.13 x 10^-3 | 60 (58-93)           | 95 (75-99)           |
| AN-GFR > 60    | ROIs           | 1.8 ± 0.10 x 10^-3 | 60 (58-93)           | 95 (75-99)           |
| AN-GFR > 60    | WP             | 0.003             |                      |                      |

Pearson correlation test was used when the distribution was normal. The sensitivity and specificity values were determined from a 2 x 2 table. The confidence interval was 95%. The results were accepted as statistically significant for p < 0.05.

Results

The age and gender distribution among AN, CKD, and HV groups were similar (p = 0.058 and p = 0.15, respectively).

Morphological evaluation

There was no major MRI-artifact on the images. The parenchymal band was detected for one of the AN patients, and the parenchymal scar was detected for two of the CKD patients. For all cases, distension was not seen in the collecting duct system. Cortical cysts were observed on 11 of the AN patients with a diameter varying from 6.8 to 48 mm, on 15 of the CKD patients with a diameter varying changing from 7 to 44.3 mm and on 10 of the control group with a diameter varying from 5 to 30 mm.

Functional evaluation

The ADC values were presented in Table 3. According to the mean ADC values, the ROIs method differentiated AN-CKD and AN-HV (p = 0.007 and p = 0.002, respectively), the whole renal parenchyma (WP) method differentiated AN-HV (p = 0.012). However, none of the methods could differentiate CKD-HV (p > 0.05).

We investigated the differentiation of AN from CKD and HV groups according to the ROC analysis (Tables 4 and 5). Cut-off ADC values for the two methods were calculated separately. Neither of the methods could differentiate CKD-HV groups. Therefore, ROC analysis of CKD-HV could not be presented.

The patients in AN and CKD groups were classified according to the threshold value of GFR 60 mL/min. The GFR values of 10 (35.7%) patients with AN and 18 (64.3%) patients with CKD were below 60 mL/min, and 14 (87.5%) of AN patients and 2 (12.5%) of the CKD patients had GFR values above 60 mL/min. The ADC value differences between the AN groups according to this GFR threshold were not significant (ROIs = 0.22, WP = 0.45, respectively). There were only two patients with GFR > 60 mL/min in the CKD group, therefore, no comparison could be made. The ADC values of 14 AN patients with GFR > 60 mL/min were found significantly lower than the HV using two methods (Table 6).

The mean value of protein/creatinine in spot urine was 444,833 ± 13,587 in the AN group and 0.78 ± 417,827 in the CKD group. The correlation of protein-uria-ADC values in AN patients was determined with ROIs methods (ROI: r = 0.565, p = 0.004). The ADC values decreased when proteinuria increased. No correlation was detected between proteinuria-ADC values in the CKD group (p > 0.05).

Discussion

The incidence of secondary (Amyloid A – AA) amyloidosis in western nations ranges from 0.5% to 0.86% in autopsy series. The kidney is affected in 80% of secondary amyloidosis cases. A biopsy is the most appropriate diagnostic method of secondary renal amyloidosis. However, a complication of hemorrhage and invasiveness should be considered. Therefore, non-invasive diagnosis of secondary renal amyloidosis is a valuable possibility. Besides, early diagnosis can delay the progression of the disease.
In the differentiation of AN patients from HV, the sensitivity of the two methods ranges from 83% to 79% and the specificity from 70% to 65%. Similarly, AN patients could be separated from CKD patients. The ideal method for differentiating AN from CKD was ROIs with its highest sensitivity (79%) and specificity (60%) rates.

As mentioned previously, renal biopsy is the most successful diagnostic method of amyloidosis. However, since the deposition in kidneys is not homogeneous, diagnosis cannot be made if amyloid deposits are not adequate or scant in the tissue sampling. Such cases sometimes are misdiagnosed as minimal-change disease. The diagnostic methods of amyloidosis other than biopsy thus gain importance. DW-MRI has been used for the diagnosis of diffuse renal diseases. Among its advantages are that it requires no contrast, contains no radiation and provides quantitative assessment owing to the ADC map. Additionally, DW-MRI is no more expensive than biopsy.

The fall in ADC values in AN patients is thought to be the result of restriction of water molecule movements in extravascular and extracellular areas because of glomerular sclerosis, tubular atrophy, interstitial fibrosis, and randomly distributed amyloid fibrils in the mesangium, basement membranes, and the interstitium.

In the literature, there are some articles about DW-MRI of the kidneys. Thoeny et al. demonstrated that patients with renal failure had lower ADC of the cortex and medulla than volunteers. Fukuda et al. showed also that the patients with high serum creatinine levels had lower ADC values in comparison to HVs.

In the presented study, ADC values of AN patients below and above of GFR threshold of 60 mL/min were not different. The number of the patients in the CKD group was insufficient for comparison with the AN group according to GFR values. In addition, ADC values of AN patients in different stages did not show any differences. This outcome may be due to lack of parallelism between the severity of renal involvement and GFR values in AN patients. In other words, GFR may not represent the severity of renal amyloidosis.

As mentioned previously, amyloid deposition in the kidney is not homogeneous. Therefore, measured ADC values do not represent the whole renal parenchyma (WP) so this may be the cause of disparity between ADC and GFR values.

In contrast to the literature, CKD-HV differentiation could not be obtained by any of the ADC measurement methods. Xu et al. found the ADC values in the CKD group were lower than that found in the HVs. In that study, there was no significant difference in the ADCs of the patients with an sCr level below the threshold (2.40 ± 0.28 × 10⁻³ s/mm², 2.52 ± 0.22 × 10⁻³ s/mm²; p > 0.05) when compared with the HVs. Thoeny et al. measured both the high and low b values from the cortex and medulla. They divided the patients into two groups according to serum creatinine level (a threshold of 2.5 mg/dL [221 μmol/L] was used). The patients with a creatinine level lower than this threshold had ADC values lower (except the ADC-high in the medulla) than those in HVs. ADC values, except for ADC-high in the medulla, were significantly different in patients with a creatinine level higher than 2.5 mg/dL [221 μmol/L] when compared with the volunteers. Fukuda et al. observed a decrease in ADC values in patients with high serum creatinine values, but in the medulla, the ADC values of the normal and diseased kidneys demonstrated overlapping. The ADC values obtained from the medulla were not different from the controls in these two studies. Therefore, obtaining the ADC values from the mesorenal or corticomedullary area in our study instead of the medulla may be the reason for the result of being unable to distinguish CKD from HV.

The ADC values of 14 AN patients with GFR >60 mL/min were significantly lower than HV. This means AN patients can be separated from HV with ADC values even when GFR values are above 60 mL/min. Karadeli et al. reported that DW-MRI can determine the early involvement of the kidney in FMF patients. Theony et al. found lower ADC values (except for the high ADC in the medulla) of the patients with serum creatinine levels below 2.5 mg/dL compared to HVs.

Proteinuria is present in most of the patients with renal amyloidosis and it is an important prognostic factor. The correlation was moderate and negative with the ROIs method, meaning that while proteinuria increases, ADC values decrease. A proteinuria-ADC correlation was not investigated before in the literature. The ADC-proteinuria correlation supports ADC measurement as an objective method for use not only in the diagnosis of renal amyloidosis but for follow-up of patients.

A correlation between ESR and ADC values was not obtained in any of the groups. ESR is commonly used to monitor inflammation in patients having acute and chronic inflammatory disease. There is an underlying chronic inflammation and neoplasia in secondary amyloidosis. Furthermore, it has been shown that proteinuria decreases when the underlying inflammation stops. The absence of correlation between ADC values and ESR indicates that the renal ADC values are not closely correlated with the activation of inflammation causing the disease.

Xu et al. calculated the renal ADC values by using circular ROI indicators and drawing the whole parenchyma on images on CKD patients and HVs. They did not
observe a significant difference between the two methods. In the present study, two methods were compared and a high correlation was found between the ROIs and WP methods. Accordingly, since there is no significant difference in ADC values obtained by these two methods, they can substitute for each other.

The most important limitation of our study is the number of patients. The number of patients grouped in stages was low. Therefore, the stages could not be correlated. Additionally, DW-MRI exams were achieved by using only one $b$ value of 1000 s/m$^2$. Therefore, we did not investigate the differentiation of other $b$ values. Correlation of ADC values and pathological specimens was not made because of the heterogeneous involvement of the renal parenchyma in renal amyloidosis.

In conclusion, DW-MRI is a non-invasive and easily applicable method which helps to diagnose secondary AN and to differentiate renal amyloidosis from other CKDs. ROIs had the highest sensitivity and specificity for assessing the involvement of renal amyloidosis. MR diagnosis of AN may obviate the necessity of a renal biopsy for diagnosis.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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