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

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Aims and objectives

Amyloidosis is a disease in which organ dysfunction occurs as a result of deposition of protein deposits in the form of insoluble fibrils in the extracellular area of tissues (1-4). Immunoglobulin light chain (AL), immunoglobulin heavy chain (AH), amyloid A (AA), hereditary amyloidosis, senile systemic amyloidosis and #2-microglobulin (#2m) amyloidosis exist among the major types of amyloidosis (5). Secondary amyloidosis, can arise as a complication of any kind chronic inflammatory, infectious and neoplastic diseases as rheumatoid arthritis, familial Mediterranean fever (FMF), inflammatory bowel disease (6-9).

Renal involvement is seen in almost every patient. Unless it is treated, it generally results in end-stage renal failure (1-4,10). 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 in amyloid deposition should be early diagnosis, if possible without biopsy.

Apart from renal tumors (11-16), studies were done using diffusion weighted magnetic resonance imaging (DW-MRI) on diffuse renal diseases such as ureteral obstruction (17), renal artery stenosis (18-20), hydronephrosis (21), pyelonephritis (21-23) and chronic kidney disease (20-22, 24-28). 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.

The purpose of this study is to compare ADC values in secondary renal amyloidosis with healthy group and cases having non-diabetic chronic kidney disease (CKD) without material deposition and to evaluate the effectiveness of DW-MRI on the diagnosis of renal involvement of secondary amyloidosis.

Methods and materials

The DW-MRI evaluations were conducted after obtaining the approval from the local ethics committee and from the participants. Moreover, the values of blood creatinine (Cr), potassium (K), erythrocyte sedimentation rate (ESR) and protein/creatinine in spot urine were tested for all participants.

Participants

Twenty four secondary amyloid nephropathy patients diagnosed by gingiva and renal biopsy [7 women, 17 men; mean age 49.67 ± 17.9 (min-max, 25-82)] 20 non-diabetic
CKD patients [12 women, 8 men; mean age 55.89 ± 13.796 (min-max, 29-80)] and 20 healthy controls [12 women, 8 men; mean age 45.74 ± 14.282 (min-max, 18-73)].

Food and water restriction were not done before imaging. All of the participants had normal fluid volume status. Blood and urine tests were performed in the same week with the MRI examination.

All CKD patients and 13 amyloid nephropathy patients were receiving hypertension treatment, and their blood pressures were in normal range. Renal artery stenosis was excluded by Doppler ultrasonography.

MR Imaging

The study was carried out with 1.5-T MRI (Optima 450W, General Electric Medical Systems, USA). The patients were examined in supine position with twelve channelled body coil. Using respiratory triggering technique, the examination was conducted on coronal plan with Propeller T2, diffusion weighted 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, FOV 400x400, matrix size 288x288, TE 82.1 ms, TR 4000 ms and flip angle 160°. In diffusion weighted examination, b value was chosen as 1000 s/mm$^2$. 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 380x380, slice thickness 5 mm, interslice gap 1 mm, matrix 256x256, bandwidth 250 kHz and NEX 4.

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

ADC Calculation Techniques

ADC measurements were performed on mesorenal area as in some previous studies (31,28). The image resolution was not sufficient to differentiate cortex and medulla since the diffusion images were captured at high b (b=1000 s/mm$^2$) value. Thus, region of interest (ROI) indicators were placed on corticomedullar junction (16,28). 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. 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 and without fat saturation, and the results of both methods were compared. At the end, four ADC means were obtained from each patient. These are:
1. Mean of region of interests (ROIs)
2. Mean of fat saturated region of interests (fsROIs)
3. Whole parenchyma (WP)
4. Fat saturated whole parenchyma (fsWP)

**Figure 1a.** In the first method, measurement was performed on diffusion weighted images by placing region of interest (ROI) indicators on corticomedullar junction (with fat saturated and ADC map, respectively).  **1b.** In the second method, ADC measurement was performed on diffusion weighted images by drawing all parenchyma.

**Fig. 1:** fig 1

**References:** Gunay Rona

**Statistical Analysis**

Furthermore, 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-Squared or Fisher Exact test.
Results

Morphological Evaluation

Parenchymal band was detected on the left kidney of one of the amyloid nephropathy patients, and parenchymal scar was detected on the left kidney of two of the CKD patients. For all cases, distension was not monitored on the collecting duct system. Cortical cysts were observed on 11 of the amyloid nephropathy patients with a diameter changing from 6.8 mm to 48 mm, on 15 of the CKD patients with a diameter changing from 7 mm to 44.3 mm and on 10 of the control group with diameter changing from 5 mm to 30 mm.

Functional Evaluation

ADC results obtained by fsROIs and WP measurement methods were found to be closely correlated (p<0.05, ICC 0.960).

No significant difference was found for the age distribution between the groups (p>0.05). Age distribution was not homogenous within the groups. No association was found between age and gender and ADC values (p>0.05).

Regarding the four measurement methods (ROIs, fsROIs, WP, fsWP), the ADC mean of amyloid nephropathy group was found significantly lower than that of CKD group. Furthermore, the ADC mean of CKD group was found significantly lower than that of the control group (p<0.05). These are presented on Table 3 and Figure 3 respectively.

Table 3. The mean ADC values of groups calculated with four measurement methods and minimum & maximum interval.

<table>
<thead>
<tr>
<th></th>
<th>ROIs</th>
<th>WP</th>
<th>fsROIs</th>
<th>fsWP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Control</td>
<td>2.1x10^-3±0.58x10^-3</td>
<td>1.9x10^-3±0.18x10^-3</td>
<td>1.9x10^-3±0.13x10^-3</td>
<td>1.9x10^-3±0.15x10^-3</td>
</tr>
<tr>
<td>Group</td>
<td>(1.6x10^-3-2.2x10^-3)</td>
<td>(1.7x10^-3-2.4x10^-3)</td>
<td>(1.6x10^-3-2.2x10^-3)</td>
<td>(1.7x10^-3-2.3x10^-3)</td>
</tr>
<tr>
<td>Amyloid Nephropathy</td>
<td>1.8x10^-3±0.11x10^-3</td>
<td>1.8x10^-3±0.12x10^-3</td>
<td>1.8x10^-3±0.10x10^-3</td>
<td>1.8x10^-3±0.11x10^-3</td>
</tr>
<tr>
<td>Disease</td>
<td>(1.6x10^-3-2x10^-3)</td>
<td>(1.6x10^-3-2x10^-3)</td>
<td>(1.6x10^-3-2.2x10^-3)</td>
<td>(1.6x10^-3-2.3x10^-3)</td>
</tr>
<tr>
<td>Chronic Kidney</td>
<td>1.9x10^-3±0.18x10^-3</td>
<td>1.9x10^-3±0.20x10^-3</td>
<td>1.9x10^-3±0.16x10^-3</td>
<td>1.9x10^-3±0.21x10^-3</td>
</tr>
<tr>
<td>Disease</td>
<td>(1.6x10^-3-2.3x10^-3)</td>
<td>(1.5x10^-3-2.3x10^-3)</td>
<td>(1.7x10^-3-2.2x10^-3)</td>
<td>(1.7x10^-3-2.5x10^-3)</td>
</tr>
</tbody>
</table>

Fig. 2: Table 3

References: Gunay Rona
Figure 3. The ADC values of groups calculated with four measurement methods - ROIs (blue), fsROIs (green), WP (light green), and fsWP (purple) respectively. (ROI: Region of interest, fs: fat-saturated, WP: Whole parenchyma, CKD: Chronic Kidney Disease).

References: Gunay Rona

No association was found between ADC and GFR or blood Cr values in the amyloid nephropathy and CKD groups (p>0.05). There was no difference in the ADC means with respect to disease stage between amyloid nephropathy and CKD groups. Additionally, no association was found between the ADC values and ESR for the three groups (p>0.05).

The amyloid nephropathy group can be distinguished from the control group by all ADC measurement methods used in ROC analysis. Moreover, the amyloid nephropathy group can be distinguished from the CKD group using the ADC values with ROIs and fsROIs methods. However, the CKD group cannot be distinguished from the control group. Among the ADC measurement methods, the highest sensitivity and specificity together belong to ROIs whose values are 79% and 85% respectively as provided in Table 4.
Table 4. Cut-off values, sensitivity and specificity of measurement methods in amyloid nephropathy.

<table>
<thead>
<tr>
<th></th>
<th>Cut-off value</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROIs</td>
<td>$1.8 \times 10^{-3}$</td>
<td>79</td>
<td>85</td>
</tr>
<tr>
<td>fsROIs</td>
<td>$1.8 \times 10^{-3}$</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>WP</td>
<td>$1.9 \times 10^{-3}$</td>
<td>79</td>
<td>70</td>
</tr>
<tr>
<td>fsWP</td>
<td>$1.9 \times 10^{-3}$</td>
<td>83</td>
<td>65</td>
</tr>
</tbody>
</table>

Fig. 4: Table 4

References: Gunay Rona

The ADC means of the amyloid nephropathy patients (n=14), whose GFR value is above 60, were found lower than that of the control group with all four measurement methods (p<0.05).

Negative correlation was detected between the ADC means obtained by all measurement methods and protein/creatinine values in spot urine in the amyloid nephropathy group (n=24) (Table 5).

Table 5. The correlation between ADC values of the measurement methods and protein/creatinine values in spot urine in the amyloid nephropathy group.
In the CKD group, a high negative association was found with Na in ROIs (p=0.005, r=-614) and WP method (p=0.011, r=-567). No association was found between K and ADC means for the three groups with all measurement methods (p>0.05).

### Conclusion

**DISCUSSION**

DW-MRI has been used for the diagnosis of diffuse renal diseases without any limitation (11-28). Requiring no contrast, containing no radiation and providing quantitative assessment owing to ADC map are its advantages (16, 29).

There is no standard b value for abdominal examination in the literature. Thoeny et al. reported that examinations conducted with high b values might be useful for assessing pathologies such as renal fibrosis (30).

The ADC values, obtained by circular ROI indicators and whole parenchyma drawing method on images with and without fat saturation were compared. There is no study on this subject that compares ADC values obtained from images with and without fat saturation.

In the present study, four ADC averages were compared and high correlation was found between fsROIs and WP. Accordingly, since there is no significant difference between ADC values obtained by these two methods, they can substitute each other.

In parenchyma drawing method, more parenchymal area is reflected. However, it is technically more difficult in cases such as dysmorphic and/or multi-cystic kidney.

<table>
<thead>
<tr>
<th></th>
<th>p value</th>
<th>r value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROIs</td>
<td>0.007</td>
<td>-538</td>
</tr>
<tr>
<td>WP</td>
<td>0.022</td>
<td>-465</td>
</tr>
<tr>
<td>fsROIs</td>
<td>0.004</td>
<td>-565</td>
</tr>
<tr>
<td>fsWP</td>
<td>0.006</td>
<td>-548</td>
</tr>
</tbody>
</table>

**Fig. 5**: Table 5

**References**: Gunay Rona
Furthermore, the probability of inclusion of pararenal fat tissue or collecting duct system into the measurement is higher in this method. Moreover, amyloid nephropathy diagnosis is made with higher sensitivity and specificity with ROIs method compared to fsROIs method. Considering these results, it is thought that the measurement method by ROIs indicators on images without fat saturation is more suitable for evaluation.

The fall in ADC values was supposed to be the result of restriction of water molecule movements in extravascular area because of glomerular sclerosis, tubular atrophy and interstitial fibrosis in renal parenchyma at chronic kidney disease (20,22, 26,27,28,31). The reason why ADC values of amyloid nephropathy group are lower than the other two groups could be because of the deposition of amyloid proteins in kidney in addition to the changes in parenchyma caused by chronic kidney disease.

It was found that the ADC values of stage 1 and stage 2 renal amyloidosis patient group with GFR value over 60 ml/min were significantly lower than the control group. This results show that amyloid deposition affects ADC values even in the early stages. Furthermore, the fact that amyloid deposition amount is not correlated with organ dysfunction (32, 33) suggests that ADC values are affected by the amount of amyloid deposition.

No correlation was detected between the ADC values, GFR and serum creatinine levels in secondary amyloid nephropathy and CKD groups. In some of the previous studies, correlation between serum creatinine (20,22,34), GFR (26,27,31) and renal ADC values was revealed. The reason of this discrepancy, is the selection of different b values and eventhough there is a low probability they may be associated with patient characteristics.

Proteinuria is accepted as an independent risk factor for cardiovascular and renal diseases and it shows end organ damage (35). A moderate negative correlation was detected between protein/creatinine values in spot urine and ADC values of kidney parenchyma with all measurement methods in amyloid nephropathy patients. This finding shows that measuring ADC values from kidney parenchyma is useful and feasible method since it indicates the intensity of renal involvement and prognosis of amyloid nephropathy patients.

There is an underlying chronic inflammation and neoplasia in secondary amyloidosis. Furthermore, it is shown that proteinuria decreases when the underlying inflammation stops (36-38). The absence of correlation between ADC values and ESR indicates that renal ADC values are not correlated with the activation of inflammation which is the cause of the disease.

The association between blood Na and ADC values has not been studied before. In this study, negative correlation was detected between ADC values measured with ROIs and
WP methods and serum Na levels in the CKD group. It is thought that this is caused with the transition of water molecules from the extracellular area to the high osmolarity intracellular area and to the vascular bed results in narrowing of the extracellular area.

The low number of patients, evaluation with only one b value, the disuse of other deposition kidney diseases are the limitation of this study.

In conclusion, DW-MRI is a non-invasive and easily applicable method which helps diagnose secondary amyloid nephropathy at an early stage.

**Personal information**

**References**


