Levels of Apelin-12, AT1R, and AGT are correlated with degree of renal fibrosis in patients with immunoglobulin A nephropathy

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Background: To explore the relationship between the degree of renal fibrosis in patients with immunoglobulin A nephropathy (IgAN) and their levels of Apelin-12, Average Optical Density of angiotensin II type 1 receptor (AOD AT1R), and angiotensinogen (AGT).

Methods: A total of 156 patients with IgAN diagnosed by renal biopsy in our hospital were selected and divided into a T0 group (54 cases), T1 group (49 cases) and T2 group (53 cases). The levels of Apelin-12, AT1R, and AGT were compared among the three groups, and the relationship between the above three indicators and degree of renal fibrosis was analyzed among patients with IgAN.

Results: The AOD AT1R and AGT level in the T2 group and T1 groups were significantly higher than those of the T0 group, and the Apelin-12 level of patients in the T1 group and T2 groups were significantly lower than that in T0 group. Significances of the same trend were observed among all the above indicators between the T2 group and T1 group. ROC curves showed that when the cutoff value of Apelin-12 was 2.36 μg/L, the area under curve (AUC), sensitivity, and specificity of T0-T1-T2 were 0.889, 92.00%, and 88.00%, respectively. When the cut-off value of AOD AT1R was 0.065, the AUC, sensitivity, and specificity were 0.706, 76.00%, and 76.00%, respectively, and when the cut-off value of AGT was 47.26 ng/mL, the AUC, sensitivity, and specificity were 0.899, 84.00%, and 88.00%, respectively. When the cutoff value of Apelin-12 was 0.92 μg/L, the AUC, sensitivity, and specificity of T0-T1-T2 were 0.819, 84.62%, and 87.50%, respectively, and when the cutoff value of AOD AT1R was 0.079, the AUC, sensitivity, and specificity were 0.699, 76.92%, and 79.17%, respectively. When the cut-off value of AGT was 92.96 ng/mL, the AUC, sensitivity, and specificity were 0.893, 84.62%, and 91.67%, respectively.

Conclusions: Apelin-12 decreased with disease progression, while AT1R and AGT increased. The changes of levels of Apelin-12, AT1R, and AGT have certain significance in judging the degree of renal fibrosis in patients with IgA nephropathy, and the change of level of AGT has the highest correlation with the degree of renal fibrosis.

Keywords: Apelin-12; angiotensin II type 1 receptor; angiotensinogen (AGT); immunoglobulin A nephropathy (IgAN)
Introduction

Immunoglobulin A (IgA) nephropathy (IgAN) is a kind of immune complex nephritis in which IgA deposits in the mesangial area of the glomerulus (1-3). IgAN is the most prevalent primary glomerular disease worldwide and in China, IgAN patients account for about 45% of primary glomerular disease (4-7). Studies have shown that renal fibrosis is an important factor affecting the progression and prognosis of IgAN (8,9). In the present study, we examined the levels of Apelin-12, angiotensin II Type 1 receptor (AT1R), and angiotensinogen (AGT) in IgAN patients with different degrees of renal fibrosis and discussed the relationship between the above indicators and the degree of kidney fibrosis of IgAN patients.

We present the following article in accordance with the STARD reporting checklist (available at http://dx.doi.org/10.21037/apm-21-1059).

Methods

Patients

One hundred and fifty-six patients with IgAN diagnosed by renal biopsy in our hospital were selected. According to the MEST-C criteria in the updated Oxford Classification of IgA Nephropathy (10), patients were divided into a T0 group (54 cases), T1 group (49 cases), and T2 group (53 cases). This study was approved by the ethics committee of Sichuan Provincial People’s Hospital. The approval number was not provided, as this was a retrospective study. Individual consent for this retrospective analysis was waived. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The inclusion criteria were all of the following: Age >18, diagnosed with IgAN via biopsy, and no glucocorticoid treatment before biopsy. The exclusion criteria were any of the following: Secondary nephropathy caused by systemic lupus erythematosus, hepatitis B, or Henoch-Schönlein purpura; renal vascular stenosis; coronary heart disease, pulmonary hypertension, arrhythmia; patients with incomplete clinical data. There was no significant difference in gender, age, and body mass index between the two groups of patients (Table 1, P>0.05).

Renal fibrosis

The degree of renal fibrosis was classified by the updated Oxford Classification of IgA Nephropathy based on the degree of cortical tubule atrophy or renal interstitial fibrosis area (10). In the T0 group cortical tubule atrophy or the renal interstitial fibrosis area was ≤25%. In the T1 group, cortical tubule atrophy or the kidney interstitial fibrosis was >25% and ≤50%, and in the T2 group, cortical tubule atrophy or renal interstitial fibrosis were >50%.

Samples and tests

Blood from the anterior cubital vein (5 mL) of each IgAN patient was collected on an empty stomach, centrifuged at 3,200 r/min to harvest the serum, and stored in a refrigerator at −80 °C for later use. On the day of admission, 15 mL of clean midstream urine was collected, cooled at room temperature, centrifuged at 2,800 r/min, then refrigerated at −80 °C for later use. Enzyme Linked Immunosorbent Assay (ELISA) was used to detect the levels of Apelin-12 and AGT using the Apelin-12 ELISA kit and human AGT-ELISA kit, respectively, and all operations were performed according to the manufactures’ instructions. The expression of AT1R was determined by immunohistochemistry. The kidney biopsy tissues were routinely dehydrated and embedded in paraffin and sections with a thickness of 3 μm were harvested with a paraffin microtome. After stretching, the slides were taken out with anti-removal slides and dried for 1 h at 57 °C. Dewaxing for 10 min was then applied in xylene solution three times, and hydration for 5 min was applied with gradient alcohol five times. After 3 min of hydration in phosphate buffer solution three times, the slides were then soaked in pure water for 10 minutes, and a high-pressure repair method was performed to expose the antigens. Citric acid buffer was added to the pressure cooker as the antigen retrieval solution and 2 min after the pressure cooker started air blasting, the heating was stopped, and the solution left to cool to room temperature. After blocking with goat serum for 45 min, AT1R antibody was then added dropwise, then incubated overnight at 4 °C. The slides were then stained with secondary antibody and hematoxylin solution, rinsed with water for 15 minutes, and observed under a microscope at ×400 magnification. Image Pro-plus software was used to analyze the Average Optical Density (AOD) of the images.

Statistics

All data was analyzed using SPSS20.0 software. The measurement data was expressed as mean ± SD and the comparison between the groups was performed using one-way analysis of variance (ANOVA). The operating characteristic...
curve (ROC) was employed to analyze the predictive value of Apelin-12, AGT, AT1R in the diagnosis of renal fibrosis in IgAN patients. P<0.05 was taken as statistically significant.

**Results**

**General pathology of patients**

The systolic blood pressure (SBP), diastolic blood pressure (DBP), mean central venous pressure (MAP), urine protein quantification, and serum creatinine levels in the T1 group were significantly higher than those in the T0 group. The blood albumin level of patients in the T1 group was significantly lower than that in the T0 group, and the levels of AOD_AT1R and AGT were significantly higher than those in the T0 group. Similarly, the levels of Apelin-12 in the T2 group were significantly lower than those in the T1 group, and the levels of AOD_AT1R and AGT were significantly higher than those in the T1 group (Table 3, P<0.05).

**Comparison of Apelin-12, AOD_AT1R, and AGT levels**

The level of Apelin-12 in the T1 group was significantly lower than that in the T0 group, and the levels of AOD_AT1R and AGT were significantly higher than those in the T0 group. The ROC curve shows that when the cutoff value of Apelin-12 is 2.36 µg/L, the area under curve (AUC), sensitivity, and specificity of T0 versus T1 (T0-T1) are 0.889, 92.00%, and 88.00%, respectively; when the cutoff value for AOD_AT1R is 0.065, the AUC, sensitivity, and specificity are 0.706, 76.00%, and 76.00%, respectively; and when the cutoff value for AGT is 47.26 ng/mL, the AUC, sensitivity, and specificity are 0.899, 84.00%, and 88.00%, respectively, as shown in Table 4 and Figure 1.

**Table 1** Comparison of clinical data of patients

<table>
<thead>
<tr>
<th>Variant</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>χ²/F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>54</td>
<td>49</td>
<td>53</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td>0.091</td>
<td>0.956</td>
</tr>
<tr>
<td>Male</td>
<td>29</td>
<td>27</td>
<td>30</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Female</td>
<td>25</td>
<td>22</td>
<td>23</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age (year)</td>
<td>35.11±8.16</td>
<td>35.48±8.55</td>
<td>35.01±8.69</td>
<td>0.043</td>
<td>0.958</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.88±2.94</td>
<td>27.79±3.05</td>
<td>27.67±3.11</td>
<td>0.064</td>
<td>0.938</td>
</tr>
</tbody>
</table>

**Table 2** Comparison of laboratory indicators among patients with different degrees of fibrosis

<table>
<thead>
<tr>
<th>Variant</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>χ²/F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>54</td>
<td>49</td>
<td>53</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>128.54±11.23</td>
<td>139.51±12.64*</td>
<td>145.28±15.12**</td>
<td>22.554</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>81.63±5.33</td>
<td>86.14±6.23*</td>
<td>89.66±8.65**</td>
<td>18.275</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>96.15±12.46</td>
<td>104.94±13.75*</td>
<td>110.21±10.53**</td>
<td>17.906</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Urine protein (g/24 h)</td>
<td>1.01±0.32</td>
<td>2.52±0.47*</td>
<td>2.96±0.54**</td>
<td>273.833</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>70.16±10.74</td>
<td>115.84±21.66*</td>
<td>183.25±30.49**</td>
<td>343.547</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Blood urea nitrogen (mmol/L)</td>
<td>4.63±1.07</td>
<td>7.52±1.48*</td>
<td>10.46±2.11**</td>
<td>175.039</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Blood albumin (g/L)</td>
<td>36.83±3.49</td>
<td>32.17±3.67*</td>
<td>30.22±3.45**</td>
<td>49.368</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*, P<0.05 compared with T0; **, P<0.05 compared with T1 group. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean central venous pressure.
The diagnostic value of Apelin-12, AT1R, and AGT in T<sub>0</sub>-T<sub>1</sub> versus T<sub>2</sub> renal fibrosis

The ROC curve shows that when the cut-off value for Apelin-12 is 0.92 μg/L, the AUC, sensitivity, and specificity of T<sub>0</sub>-T<sub>1</sub> versus T<sub>2</sub> (T<sub>0</sub>-T<sub>1</sub>-T<sub>2</sub>) are 0.819, 84.62%, and 87.50%, respectively; when the cut-off value for AOD<sub>AT1R</sub> is 0.079, the AUC, sensitivity, and specificity is 0.699, 76.92%, and 79.17%, respectively; and when the cut-off value for AGT is 92.96 ng/mL, the AUC, sensitivity, and specificity are 0.893, 84.62%, and 91.67%, respectively, as shown in Table 3 and Figure 1.

### Table 3 Comparison of levels of Apelin-12, AOD<sub>AT1R</sub>, and AGT among T<sub>0</sub> group, T<sub>1</sub> group, and T<sub>2</sub> group

<table>
<thead>
<tr>
<th>Stage</th>
<th>n</th>
<th>Apelin-12 (μg/L)</th>
<th>AOD&lt;sub&gt;AT1R&lt;/sub&gt;</th>
<th>AGT (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&lt;sub&gt;0&lt;/sub&gt;</td>
<td>54</td>
<td>3.41±1.02</td>
<td>0.05±0.01</td>
<td>28.27±4.19</td>
</tr>
<tr>
<td>T&lt;sub&gt;1&lt;/sub&gt;</td>
<td>49</td>
<td>1.16±0.33*</td>
<td>0.07±0.01*</td>
<td>64.76±8.56*</td>
</tr>
<tr>
<td>T&lt;sub&gt;2&lt;/sub&gt;</td>
<td>53</td>
<td>0.74±0.21*</td>
<td>0.09±0.01*</td>
<td>120.41±20.23*</td>
</tr>
<tr>
<td>F</td>
<td>–</td>
<td>268.088</td>
<td>213.987</td>
<td>689.554</td>
</tr>
<tr>
<td>P</td>
<td>–</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*, P<0.05 compared with T<sub>0</sub> group; *, P<0.05 compared with T<sub>1</sub> group. AOD<sub>AT1R</sub>, Average Optical Density of angiotensin II type 1 receptor; AGT, angiotensinogen.

### Table 4 Diagnostic value of Apelin-12, AT1R, and AGT on T<sub>0</sub>-T<sub>1</sub>-T<sub>2</sub>

<table>
<thead>
<tr>
<th>Index</th>
<th>Cut-off</th>
<th>AUC</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Youden index</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apelin-12</td>
<td>≤2.36</td>
<td>0.889</td>
<td>92.00</td>
<td>88.00</td>
<td>0.800</td>
<td>0.768-0.960</td>
</tr>
<tr>
<td>AOD&lt;sub&gt;AT1R&lt;/sub&gt;</td>
<td>&gt;0.065</td>
<td>0.706</td>
<td>76.00</td>
<td>76.00</td>
<td>0.520</td>
<td>0.561-0.827</td>
</tr>
<tr>
<td>AGT</td>
<td>&gt;47.26</td>
<td>0.899</td>
<td>84.00</td>
<td>88.00</td>
<td>0.720</td>
<td>0.781-0.966</td>
</tr>
</tbody>
</table>

AOD<sub>AT1R</sub>, Average Optical Density of angiotensin II type 1 receptor; AGT, angiotensinogen; AUC, area under curve.

### Discussion

IgAN is one of the main causes of renal fibrosis and end-stage renal failure. Renal fibrosis is manifested by the accumulation of fibroblasts, myofibroblasts, and extracellular matrix, leading to glomerular interstitial fibrosis and glomerulus sclerosis, eventually leading to the loss of renal function (3,11,12).

In this study, the SBP, DBP, MAP, urine protein quantification, and serum creatinine levels of patients in the T<sub>2</sub> and T<sub>1</sub> groups were significantly higher than those in the T<sub>0</sub> group, while the blood albumin level of patients in the T<sub>2</sub> and T<sub>1</sub> groups were significantly lower than those in the T<sub>0</sub> group. The SBP, DBP, MAP, urine protein quantification, and serum creatinine level was significantly higher in the T<sub>2</sub> group than in the T<sub>1</sub> group, while blood albumin level was significantly lower than the T<sub>1</sub> group.

When the kidney is severely damaged, renal function is significantly reduced and glomeruli are damaged, resulting in proteinuria. Proteinuria can activate the secretion of excessive inflammatory mediators and chemokines from
Changes in vasoconstriction and renal fibrosis. Activated AT1R may also promote mesangial cell proliferation and the formation of crescents, and cause glomerular sclerosis.

The renin-angiotensin system (RAS) is an important regulatory system in the human body. As the sole substrate of RAS, angiotensin II can predict the condition of the kidney. The Apelin-12 peptide is a vasodilator which binds to orphan G protein-coupled receptor proteins such as angiotensin. AT1R is distributed in blood vessels, kidneys, adrenal glands, liver, brain, and other tissues and organs, and induces smooth muscle contraction. Angiotensin II is activated by AT1R to exert its cellular and molecular effects, which can cause inflammation and a pro-fibrotic reaction, which possibly leads to an increase in the degree of renal fibrosis. In this study, the levels of Apelin-12 in the T₂ and T₁ groups were significantly lower than those in the T₀ group, and the levels of AOD_AT1R and AGT were significantly higher than those in the T₀ group. The levels of Apelin-12 in the T₂ group were significantly lower than those in the T₁ group and the levels of AOD_AT1R and AGT were significantly higher than those in the T₁ group. It seems that as the degree of renal fibrosis in patients increased, the level of Apelin-12 decreased, and the expression of AT1R and AGT increased. Apelin-12 is a newly discovered biologically active peptide that can participate in the regulation of normal physiological functions of the kidney and bind to orphan G protein-coupled receptor proteins such as angiotensin II. AT1R is activated by AT1R to exert its cellular and molecular effects, which can cause changes in vasoconstriction and renal fibrosis. Activated AT1R may also promote mesangial cell proliferation and the formation of crescents, and cause glomerular sclerosis.

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possibly could be improved when other serum indicators were introduced.

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**Footnote**

**Reporting Checklist:** The authors have completed the STARD reporting checklist Available at [http://dx.doi.org/10.21037/apm-21-1059](http://dx.doi.org/10.21037/apm-21-1059)

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**Conflicts of Interest:** All authors have completed the ICMJE uniform disclosure form (available at [http://dx.doi.org/10.21037/apm-21-1059](http://dx.doi.org/10.21037/apm-21-1059)). The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the ethics committee of Sichuan Provincial People's Hospital. The approval number was not provided, as this was a retrospective study. Individual consent for this retrospective analysis was waived. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

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