The Role of Apelin 13 in Progression of Chronic Kidney Disease

Yasemin Coskun Yavuz, 1 Can Sevinc, 1 Mustafa Saygin Deniz, 2 Serkan Yavuz, 3 Orcun Altunoren, 4 Hayriye Sayarlioglu, 5 Ekrem Dogan 6

Introduction. Apelin is an adipokine secreted by the adipose tissue and by the endothelial cells in various parts of the body. Apelin is also expressed by the glomerular arteriolar rectus and glomerular capillary cells. We evaluated the relationship between the initial serum levels of apelin 13 with the trend of glomerular filtration rate (GFR) during a 1-year follow-up of patients with chronic kidney disease (CKD).

Materials and Methods. Ninety-nine patients with CKD in the predialysis stages were included and completed the study. The demographic data, medications, and comorbidities of the patients were recorded. The relationship between the baseline apelin 13 levels and the 1-year GFR loss was evaluated.

Results. The mean 1-year GFR loss 1.6 mL/min for those with CKD stage 3, 5.1 mL/min for those with CKD stage 4, and 2.6 mL/min for those with CKD stage 5. Fifty-eight patients (58.6%) had a GFR loss less than 5 mL/min and 41 (41.4%) had a GFR loss of 5 mL/min and greater, for whom the mean apelin 13 levels were 2169 ± 1807 mL/min and 2513 ± 1920 mL/min, respectively (P = .36). There was no significant correlation between the apelin 13 levels and GFR loss (P = .35).

Conclusions. To our knowledge, this study was the first that clinically examined the relationship between apelin 13 and CKD progression. Apart from the diabetic nephropathy, several factors causing comorbidity and progression may have probably masked this potential relationship.

INTRODUCTION

In chronic kidney disease (CKD), there is chronic inflammation resulting from a number of causes such as uremia, oxidative stress, increase in the proinflammatory cytokines, decrease in the anti-oxidants, and protein energy malnutrition.1 Inflammation affects the CKD progression and mortality along with it.2 As in several other systems, apelin has also effects on the renal system. It has such impacts as the opposing negative effect on hemostasis and angiotensin II type 1 and diabetic nephropathy and renal ischemia-reperfusion balance. Its receptor is isolated in the inner layer of the outer medulla, in the arterial wall in the glomerulus and also in the tubular segments. In the studies conducted on mice, it was found that upon applying ligation on the unilateral ureter, apelin and its receptor in that part seemed to increase. Separately, the apelin level was seen to have increased in the rats on which a nephrotic
syndrome induced by adriamycin was developed. In our study, we aimed to examine the relationship between the apelin 13 levels in predialysis patients and the CKD progression.

MATERIAL AND METHODS

A total of 144 patients with a diagnosis of CKD, followed up in their CKD stages 2 to 4, along with those in stage 5 who had not undergone dialysis were incorporated in the study. Nine patients were referred for dialysis and 36 patients were lost to follow up in 1 year. The study was completed with 99 patients. Data on demographic characteristics, medications, and comorbidities were extracted from their files. Systolic and diastolic blood pressure was measured in the sitting position and the blood samples were collected. The glomerular filtration rate (GFR) calculations according to the creatinine values in the beginning and 1 year later were performed according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) formulas.

Blood samples were centrifuged, and plasma was frozen at -80°C. Serum apelin 13 levels (USCN Life Science Inc) were measured at the start of the study using an enzyme-linked immunosorbent assay method and automatic enzyme-linked immunosorbent assay microplate reader (Thermo Scientific, Finland) and also the Skanlt for Multiscan FC 2.5.1 computer program. The sensitivity proved to be 37.2 pg/mL, whereas the detection range was 98.8 pg/mL to 8000 pg/mL.

The patients were divided into the 2 groups according to the 1-year GFR loss: group 1 consisted of patients with a GFR loss of 5 mL/min and greater and group 2, a GFR loss below 5 mL/min. The difference between the groups was investigated in terms of serum apelin 13 levels. Apelin 13 levels were also with regards to proteinuria. Those with proteinuria were further grouped into 3 proteinuria levels of 1+, 2+, and 3+. The relationships between baseline serum apelin 13 levels and sex, age, duration of CKD, diabetes mellitus (DM), hypertension, coronary artery disease (CAD), administration of renin-angiotensin-aldosterone system (RAAS) inhibitors were evaluated.

RESULTS

The patients were 55 men (55.6%) and 44 women (44.4%). The mean age was 56.4 ± 15.1 years. The demographic and laboratory data of the patients are shown in Table 1. The mean apelin 13 level was 2180 ± 1875 pg/mL in the men and 2476 ± 1833 pg/mL the women (P = .43). Twenty-eight patients had DM (28.3%). There was no significant correlation between age and apelin 13 levels (P = .16). There was no significant correlation between the duration of CKD and apelin 13 levels, either (P = .49).

The apelin 13 level in those with DM was higher than in those without DM, but the difference was not significant (2681 ± 2207 pg/mL versus 2166 ± 1689 pg/mL, P = .21). Eighty-four patients (84.8%) had hypertension and 24 patients (24.2%) were followed up in the Department of Cardiology with a diagnosis of CAD. Apelin 13 levels were not significantly different between patients with and without CAD (2378 ± 1809 pg/mL versus 2395 ± 1819 pg/mL, P = .84) or between patients with and without hypertension (2316 ± 1845 pg/mL versus 2290 ± 1963 pg/mL, P = .88).

The distribution of the stages of CKD at the start and the end of the study is summarized in

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Sex</td>
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<tr>
<td>Female</td>
<td>44</td>
</tr>
<tr>
<td>Male</td>
<td>55</td>
</tr>
<tr>
<td>Age, y</td>
<td>56.4 ± 15.1</td>
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<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>96.7 ± 12.7</td>
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<tr>
<td>Serum creatinine, mg/dL</td>
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<tr>
<td>Baseline</td>
<td>2.94 ± 1.34</td>
</tr>
<tr>
<td>At 1 year</td>
<td>3.88 ± 2.50</td>
</tr>
<tr>
<td>Glomerular filtration rate, mL/min</td>
<td></td>
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<tr>
<td>Chronic Kidney Disease Epidemiology Collaboration</td>
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<tr>
<td>Baseline</td>
<td>25.2 ± 12.9</td>
</tr>
<tr>
<td>At 1 year</td>
<td>22.1 ± 14.1</td>
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<tr>
<td>Modification of Diet in Renal Disease</td>
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<tr>
<td>Baseline</td>
<td>26.1 ± 12.7</td>
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<tr>
<td>At 1 year</td>
<td>21.6 ± 15.3</td>
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<tr>
<td>Serum albumin, g/dL</td>
<td>4.14 ± 0.34</td>
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<tr>
<td>C-reactive protein, mg/L</td>
<td>9.0 ± 12.9</td>
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<tr>
<td>Uric acid, g/dL</td>
<td>7.4 ± 1.9</td>
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<tr>
<td>Hemoglobin, g/dL</td>
<td>11.8 ± 1.9</td>
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<tr>
<td>Low-density lipoprotein cholesterol, g/dL</td>
<td>100.9 ± 33.0</td>
</tr>
<tr>
<td>Duration of chronic kidney disease, mo</td>
<td>27.3 ± 20.0</td>
</tr>
</tbody>
</table>

*Values are presented as mean ± standard deviation, except for sex distribution.
Table 2. Apelin 13 levels were 1876 ± 300 pg/mL in patients with CKD stage 3, 2703 ± 324 pg/mL in patients with CKD stage 4, and 2365 ± 268 pg/mL in patients with CKD stage 5. There were no significant differences between these groups in terms of apelin 13 levels (P = .14). The extent of CKD progression was assessed based on the loss of GFR calculated with the MDRD formula for all and for each stage. The mean 1-year GFR loss was 4.5 ± 4.8 mL/min for all of the patients, 1.6 mL/min for those with CKD stage 3 (P = .18), 5.1 mL/min for those with CKD stage 4 (P < .001), and 2.6 mL/min for those with CKD stage 5 (P = .04).

There was no significant correlation between the apelin 13 levels and GFR loss (P = .35). Fifty-eight patients (58.6%) had a GFR loss less than 5 mL/min and 41 patients (41.4%) had a GFR loss of 5 mL/min and greater. The mean apelin 13 level in those with GFR loss less than 5 mL/min was 2169 ± 1807 pg/mL, whereas the mean apelin 13 level in those with a greater GFR loss was 2513 ± 1920 pg/mL (P = .36). There was no significant correlation between GFR and apelin 13 level in those with a GFR loss less than 5 mL/min (P = .06) or those with a greater loss of GFR (P = .70).

The mean apelin 13 level in 29 patients who used RAAS inhibitors was 2110 ± 1849 pg/mL, whereas the mean apelin 13 in 70 patients who did not use RAAS inhibitors was 2395 ± 1819 pg/mL (P = .50).

The patients were divided into 2 groups as 69 with proteinuria and 30 without proteinuria. While the GFR loss in those without proteinuria was 3.5 mL/min, the average GFR loss in those whose proteinuria was 3+ was 6.0 mL/min. Although the GFR loss in those with proteinuria was prominent, the difference was not significant (P = .05). Whereas 60% of the patients whose GFR loss was less than 5 mL/min had proteinuria, 78% of the patients with greater GFR loss had proteinuria. The mean apelin 13 level in those with proteinuria was 2437 ± 1869 pg/mL, whereas the mean apelin 13 in those without proteinuria was 2023 ± 1813 pg/mL (P = .85). There was no significant correlation between proteinuria level and apelin 13 level, either (P = .15).

DISCUSSION

Known for the last 20 years, apelin 13 is an adipokine determined to have been secreted in the central nervous system, placenta, heart, lungs, and kidneys in the human body. As in several other systems, apelin 13 has also effects on the renal system. It has such impacts as the opposing negative effect on hemostasis and angiotensin II type 1 and diabetic nephropathy and renal ischemia-reperfusion balance. Its receptor is isolated in the inner layer of the outer medulla in the arterial wall in glomerulus and also in the tubular segments. In the studies conducted on mice, it was found that upon applying ligation on the unilateral ureter, the apelin 13 concentration and its receptor’s expression in that part increase.4,5

Day and colleagues10 induced diabetic nephropathy in mice and found no significant change in the weight and serum glucose levels of the mice after the administration of apelin 13; however, it was observed that the glomerular hypertrophy decreased and albuminuria remained significantly unchanged after 3 months but significantly decreased with the injection of apelin 13 for 6 months. It was also observed that there was a decline in the activation of angiotensin II receptor through the use of apelin. Hence, the activation of the antioxidant system by apelin 13 was considered as being the cause of minimizing proteinuria. Pathological examination of kidneys revealed that it did not cause any change in the number of podocytes; however, it reduced proteinuria over the proximal tubule epithelial cells.10

Kamimura and coworkers published their study on 98 predialysis patients in 2012, in which adiponectin levels were not found to be correlated with GFR loss, creatinine, or albuminuria after a 12-month follow-up period.6 Leal and colleagues compared 24 hemodialysis patients and 15 patients of the control group and found that the apelin 36 levels were similar, whereas the apelin 12 levels were higher in the hemodialysis group. In fact, no correlation was found between apelin 12 and 13 and body mass index, sex, body fat rate and waist thickness, C-reactive protein, interleukin-6,
and low-density lipoprotein cholesterol. We also observed in our study that there was no correlation between the apelin 13 level and C-reactive protein and low-density lipoprotein cholesterol. Our study is the first to clinically examine this relationship, yet we could not find such a relationship in this study of ours. In our patient population, apart from the diabetic nephropathy, several factors causing comorbidity and progression may have probably caused our results to conflict with this study.

In a study comprising 60 patients with diabetic nephropathy, the serum apelin 13 level was found to be higher in diabetic patients, and a positive correlation was documented between the apelin 13 level and albuminuria. Moreover, there are studies suggesting that the apelin level in the newly diagnosed patients with type 2 DM is lower than that in the control group as well as those studies which suggest that the apelin level in the obese patients with type 2 DM is high and that it is correlated with hemoglobin A1c. Silva and coworkers had a lower rate of apelin 13 levels in patients with high starting renal replacement therapy, but could not find a direct relationship between GFR loss and apelin 13 levels. In our study, we did not determine any differences between the diabetic patients and the nondiabetic ones in terms of their apelin levels. In addition, as in the studies by Kamimura and colleagues and Garland and colleagues, we could not find a correlation between age and sex and GFR loss at the end of the 1-year follow-up. In these two studies, no relationship could be found between the use of RAAS inhibitors and GFR loss, either. However, in our study, despite the fact that there was less GFR loss in those using RAAS inhibitors (4.9 mL/min as opposed to 5.3 mL/min), this difference was still statistically nonsignificant.

There are also studies suggesting the relationship between proteinuria and CKD progression. In a study investigating the factors that affect the CKD progression, those with proteinuria were seen to have undergone a significantly more rapid progression of the disease than those who had no proteinuria at the end of the follow-up (19 months on the average). In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study, on the other hand, the risk of progressing towards end-stage kidney disease in 1513 patients with diabetic nephropathy was found to be 5.2 times greater in the patients with proteinuria.

Lorenzo and colleagues conducted a study on 333 patients and found a shorter life span without dialysis in those with proteinuria, whether or not DM was involved. They could not find a significant relationship among age, hemoglobin, uric acid level, and the presence of DM and CKD progression. In our study, we could not find any significant correlation between age, hemoglobin, uric acid level, and the presence of DM and GFR loss, either.

We also examined the relationship between proteinuria and GFR loss in our study. The GFR loss within 1 year was 3.5 mL/min on the average in those who had no proteinuria, whereas this amount was 6 mL/min in those with 3+ proteinuria; the GFR loss seemed to be more prominent in those with proteinuria; however, such a difference was not significant. In our study, the patients were evaluated as those with proteinuria and those without proteinuria, and the amount of proteinuria was evaluated as 1+, 2+, and 3+ by using the reflectance photometric method on an automatic device. Such results could have been affected by if we had studied the amount of proteinuria as the rate of protein to creatinine in the spot urine or as the protein rate in a 24-hour urine sample. Therefore, although we found more GFR loss in those with more proteinuria, we may not have found the quite well-known relationship between the GFR loss and the proteinuria level to be at significant levels.

**CONCLUSIONS**

Although there are studies on animals suggesting the apelin 13 level and the changes of glomerular and tubular structure, there is no clinical study demonstrating the relationship between the apelin level and GFR loss. In our study, we evaluated the relationship between the apelin 13 level in the predialysis CKD patient population and the 1-year GFR loss, and we were unable to find a significant relationship between these two parameters at the end of this study. This study, to our knowledge, is the first known study that examines and analyzes the relationship between GFR loss and apelin 13 level.

**CONFLICT OF INTEREST**

None declared.
REFERENCES


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