İKSSTD 2019;11(3):171-177
doi: 10.5222/iksstd.2019.77486

Araştırma / *Research Article*

Is Serum FGF-23 Associated with Subclinic Atherosclerosis in Patients with AA Amyloidosis?

AA Amiloidozlu Hastalarda Serum FGF-23 Düzeyi Subklinik Aterosklerozun Göstergesi midir?

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ABSTRACT

Objective: *Amyloid A (AA) amyloidosis is the most prevalent form of systemic amyloidosis, and is a serious condition characterized by protein-misfolding. Cardiovascular involvement is known to be a significant manifestation of the disease and common carotid artery intima-media thickness (CIMT) assessment is one of the well-recognized tools for identification of subclinical atherosclerosis. It was reported that FGF-23 may be a significant factor associated with atherosclerosis development in patients with AA amyloidosis, as well as being an independent risk factor for increased CIMT. In this study, we aimed to investigate whether elevated FGF-23 levels might be associated with CIMT levels in AA amyloidosis patients.*
Method: *We studied 63 patients with AA amyloidosis and 29 aged-matched healthy controls. All subjects' demographic data were recorded and the following parameters were measured: erythrocyte sedimentation rate, C-reactive protein, creatinine, urea, albumin, calcium, phosphate, parathyroid hormone, FGF-23, eGFR, CIMT, blood pressure and BMI.*
Results: *CIMT levels were significantly higher in AA amyloidosis patients compared to the control group (p<0.001). However, serum FGF-23 levels were similar (p=0.110). CIMT was correlated with patient age (r=0.471, p<0.001), but serum FGF-23 was not associated with CIMT in patients with amyloidosis (r=0.031, p=0.807).*
Conclusion: *Although our results suggest a lack of association between FGF-23 levels and CIMT in patients with AA amyloidosis.*

Keywords: *amyloidosis, carotid intima-media thickness, fibroblast growth factor-23, atherosclerosis*

ÖZ

Amaç: *Amiloidoz proteinlerin anormal katlantı oluşturması ile karekterize hayatı tehdit eden bir hastalıktır, Amyloid-associated (AA) amiloidoz sistemik amiloidozun en yaygın formudur. Kardiyovasküler tutulum amiloidozun en önemli klinik tezahürüdür ve karotis intima media kalınlığının ölçümü (KIMK) subklinik aterosklerozu tespit etmek için iyi tanımlanmış yöntemlerden birisidir. FGF-23 AA amiloidozda KIMK'dan bağımsız olarak subklinik ateroskleroz ile ilişkili olabileceği bildirilmiştir. Bu çalışmada amacımız, AA amiloidozlu hastalarda KIMK ile yükselmiş serum FGF-23 ile ilişkisinin olup olmadığına bakmaktı.*
Yöntem: *Çalışmaya 63 AA amiloidozlu hasta ve 29 sağlıklı kontrol dahil ettik. Tüm olguların demografik verileri, eritrosit sedimantasyon hızı, Crp, kreatinin, üre, albumin, kalsiyum, fosfat, parathormon, FGF-23, eGFR, KIMK, kan basıncı ve vücut kitle indeksleri kayıt edildi.*
Bulgular: *Karotis intima media kalınlığı AA amiloidozlu hastalarda kontrol grubuna göre anlamlı derecede fazlaydı (p<0.001). Bununla birlikte serum FGF-23 seviyesi iki grup arasında farklı değildi (p =0.110). KIMK yaş ile köreleydi (r=0.471, p<0.001), fakat serum FGF-23 seviyesi amiloidozlu hastalarda KIMK ile körele değildi (r=0.031, p=0.807).*
Sonuç: *Bizim çalışmamızda, AA amiloidozlu hastalarda KIMK ile Serum FGF-23 seviyesi arasında bir korelasyon tespit edilememiştir.*

Anahtar kelimeler: *amiloidozis, karotis intima media kalınlığı, fibroblast growth factor-23, aterosiklerozis*

Alındığı tarih: 30.01.2019
Kabul tarihi: 27.06.2019
Yayın tarihi: 30.09.2019

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INTRODUCTION

Amyloidosis is a potentially life-threatening disease characterized by protein-misfolding and the deposition of aggregated proteins in various tissues. Although there are different types of amyloidosis, amyloid A (AA) amyloidosis is the most prevalent form of systemic amyloidosis. With the promoted treatment of chronic autoimmune diseases with new drugs such as tumor necrosis factor (TNF) receptor and interleukin (IL)-6 blockers [1], the prevalence of AA amyloidosis is getting rarer in the Western world [1,2]. Meanwhile, the incidence of AA amyloidosis remains high in many developing parts of the world [3].

Many studies have shown that hyperphosphatemia, increased serum PTH, and low 1,25(OH)2 D3 levels are independently associated with increased all-cause and cardiovascular mortality in patients with end-stage renal disease [4-6]. These results have directed researchers to investigate regulation of mineral metabolism and its consequences in patients with chronic kidney disease. Fibroblast growth factor 23 (FGF-23) is a hormone secreted by osteoblasts which is an important negative regulator of phosphate and vitamin D metabolism. FGF-23 induces renal phosphate wasting by inhibiting the proximal tubular sodium phosphate cotransporter type IIa and suppresses renal expression of CYP27B1, resulting in a decrease in the synthesis of 1,25(OH)2 D3 [7]. Several studies have indicated that serum levels of FGF-23 are elevated in hemodialysis patients [5,8,9]. But, to our knowledge, there are currently no studies in the literature which have investigated FGF-23 levels in patients with AA amyloidosis.

Common carotid artery intima-media thickness (CIMT) assessment is one of the well-recognized and more easily obtainable tools for identification and monitoring of subclinical and asymptomatic atherosclerotic vascular diseases. Several large cohort studies have clearly shown a relationship between CIMT and CV events and have advised its utilization in patients with risk [10,11]. Until now, only one study investigated CIMT levels in AA patients.

As data on the association between FGF-23 and atherosclerosis are currently limited in patients with AA amyloidosis, the aim of the present study was to investigate whether elevated FGF-23 levels were associated with CIMT levels in patients with AA amyloidosis.

Patients and methods

This observational cross-sectional study was approved by Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Committee, and informed consents were obtained from all participants. We studied 63 patients with AA amyloidosis who were seen consecutively at the Nephrology Clinic of Istanbul Medeniyet University, Goztepe Training and Research Hospital, between April 2018 and May 2018. As a control group, 29 age-matched healthy subjects were enrolled. The diagnosis of AA was established by means of renal, gingival, rectal, duodenum or bone marrow biopsies. Patients with diabetes mellitus, hypertension, liver diseases, hyperthyroidism, hypothyroidism, rheumatoid hematological disorders, malignancy and acute/chronic infections were excluded from the study. Demographic data, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatinine, urea, albumin, calcium, phosphate, parathyroid hormone (PTH), FGF-23, eGFR, CIMT, blood pressure and BMI values of all patients were assessed and recorded. FGF-23 was determined using a double sandwich ELISA kit used according to manufacturer instructions (Cat. No: SEA746Hu, Wuhan USCN Business Co., USA). Values were expressed in pg/mL. Patients' eGFR values were calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation: eGFR = [141 × min (SCr (mg/dL)/k, 1)α × max (Scr/k, 1)-1.209 × 0.993 age × 1.018]; where k is 0.7 in females and 0.9 in males, while α is (-0.329) in females and (-0.411) in males [12].

CIMT measurement

All CIMT measurements were performed with a 5-12 MHz frequency superficial probe using a M-Turbo ultrasonography device (SonoSite Inc., Bothell, WA, USA). The common carotid arteries were evaluated while the patient was lying supine with his/her head tilted slightly upward from the midline position. Carotid intima-media thickness (CIMT) was measured from 1 cm proximal to the bifurcation region on each side as described previously (13). The distance between the media–adventitia interface and the lumen–intima interface was defined as CIMT. Mean CIMT values of all patients were calculated as the mean of triplicate measurements of each carotid artery.

Statistical analysis

Data were evaluated using the Statistical Package for Social Sciences (SPSS) version 21.0 software for Windows. The normality of distribution of continuous variables was determined by the Shapiro–Wilk test. Continuous variables were given as median and interquartile range [IQR] or mean ± standard deviation (SD), with regard to normality of distribution. We analyzed descriptive statistics using the Mann-Whitney U test or independent samples t test. Correlation analyses were performed by calculation of Spearman's rho. p-value <0.05 was considered as the level of statistical significance.

RESULTS

A total of 63 (68%) patients with AA amyloidosis and 29 (32%) healthy controls were included in the study. Female/male ratios were 29 (55%)/34 (45%) in the amyloidosis group, and 21 (72%)/8 (28%) in the control group. Mean ages were 49.61±14.79 years in the amyloidosis group and 48.34±.01 years in the control group. There were no statistically significant differences between the groups in terms of the age, systolic blood pressure (SBP), and diastolic blood pressure (DBP), (p>0.05). The amyloidosis patients had lower BMI values compared to healthy controls (p<0.001) [Table 1].

Table 1. Demographic characteristics and clinical measurements in amyloidosis and healthy control groups.

Parameter (Unit)	Amyloidosis	Control	p-value
Age (years)	51 (36-60)	48 (43-54)	0.366
BMI (kg/m^2)	24.8 (22.4-26.2)	28.15 (25.9-32.6)	<0.001
SBP (mmHg)	120 (110-140)	120 (120-135)	0.609
DBP (mmHg)	80 (70-85)	80 (70-80)	0.434
FGF23 (mmol/L)	13.61 (8.5-19.9)	17.7 (9.9-27.0)	0.110
CIMT (mm)	0.8 (0.6-1)	0.6 (0.5-0.7)	<0.001
CRP (mg/dL)	1.32 (0.56-2.80)	0.33 (0.33-0.74)	<0.001
ESR	63 (31-97)	5 (4-8)	<0.001
Creatinine (mg/dL)	1.5 (0.89-2.66)	0.68 (0.63-0.82)	<0.001
Urea (mg/dL)	51 (36-89)	25 (21-30)	<0.001
eGFR (mL/min/1.73 m^2)	48.4 (23.6-94.2)	102.5 (91-108)	<0.001
Albumin (g/dL)	3.2 (2.5-4.0)	4.6 (4.5-4.8)	<0.001
PTH (pg/mL)	71.3 (32.8-142)	46.95 (36-61)	0.044
Ca (ng/mL)	8.7 (8.2-9.2)	9.5 (9.1-9.7)	<0.001
P (ng/mL)	3.8 (3.4-4.6)	3.4 (3.0-3.7)	0.001

BMI: body mass index; CIMT: carotid intima-media thickness; CRP: C-reactive protein; Ca: Serum calcium; DBP: diastolic blood pressure; ESR: erythrocyte sedimentation rate; P: Serum Phosphate; PTH: Parathyroid Hormone; SBP: systolic blood pressure.

The FGF-23 levels of the amyloidosis patients and the control group were similar (13.61 [8.5-19.9] vs. 17.7 [9.9-27.0] mmol/L, p=0.110). CIMT values of patients with amyloidosis were significantly higher than those of the control group (0.82±0.20 vs 0.61±0.24 mm, p<0.001) [Table 1].

CRP, ESR, creatinine, urea, PTH, and serum phosphate levels were significantly higher in the patient group compared to healthy controls (p<0.05, for each comparison). Also, albumin, serum calcium and eGFR values were significantly lower in those with amyloidosis (p<0.001) [Table 1].

There was no correlation between FGF-23 and CIMT values (r=0.031, p=0.807) or between FGF-23 and eGFR values (r=0.032, p=0.802) in AA patients (Figure 1). There was a positive correlation between CIMT values and age in AA patients (r=0.471, p<0.001) (Figure 2). Also, there were no correlations between BMI, CRP, ESR, creatinine, PTH, calcium, phosphate levels and CIMT values in AA patients (p>0.05). Similarly, there were no correlations between FGF-23 levels and parameters such as BMI, CRP, ESR, creatinine, PTH, calcium and phosphate in AA patients (p>0.05).

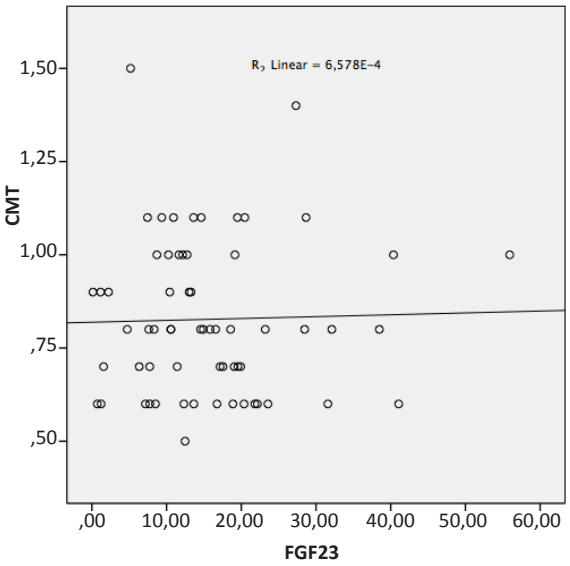

Figure 1. The relationship between serum FGF23 levels and CIMT levels in patients with amyloidosis.

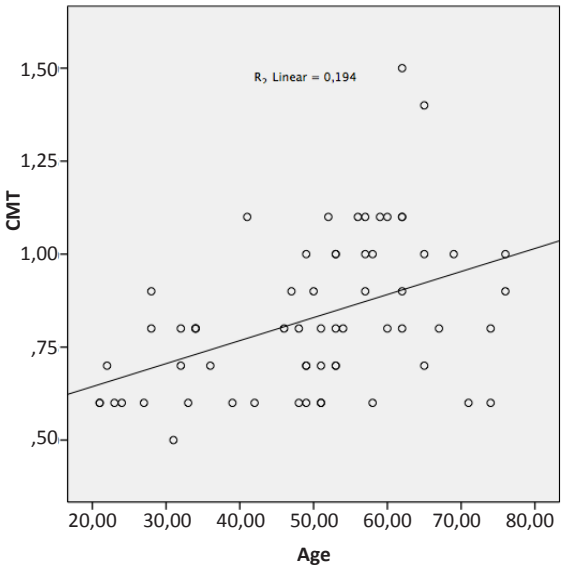

Figure 2. The relation between CIMT levels and the age of the patients with amyloidosis.

DISCUSSION

Chronic inflammation is a hallmark of AA amyloidosis. Considering that increased CIMT has been suggested to reflect constant systemic inflammation [14], and the fact that high FGF-23 concentrations are reportedly a significant independent risk factor for increased CIMT [15]; we hypothesized that a relationship between FGF-23 levels and CIMT may exist in patients with AA amyloidosis. Similar studies which have evaluated FGF-23 and CIMT levels in patients with AA amyloidosis are few; however, various studies have investigated CIMT value in patients with familial Mediterranean fever (FMF), a disease characterized with chronic inflammation. Several of these studies have reported increased CIMT values in FMF patients [16-18]. However, Sari et al. found no increase in CIMT in FMF patients [19].

To our knowledge, this is the first study to investigate FGF-23 and its association with CIMT in patients with AA amyloidosis. The FGF-23 levels of patients were not different from the levels measured in controls. However, we found that CIMT was increased in the AA amyloidosis group compared to the control group. There was no correlation between the FGF-23 and CIMT levels in the patients with AA amyloidosis.

Many other studies have also investigated FGF-23 levels in different diseases. FGF-23 levels are known to progressively increase in patients with CKD. Furthermore, FGF-23 levels are generally 100- to 1000-times higher than the normal range at the advanced stages of CKD [29]. Also, there is an association between increased FGF-23 levels and mortality rates among patients on hemodialysis (HD) treatment [20,21]. These findings may be explained by the reported correlation between FGF-23 values and peripheral vascular, aortic and coronary artery calcification in patients who undergo HD [21,22]. However, in contrast, in their study Scialla et al., reported that FGF-23 did not induce arterial calcification [23].

In a study on diabetes mellitus (DM), Hu et al. suggested that a first-degree family history of diabetes contributes to increased serum FGF-23 levels. However, only those with serum FGF-23 levels in the upper quartile were found to have an increased CIMT, indicating that subclinical atherosclerosis was associated with excessively increased FGF-23 levels [24]. In another study on DM patients, Biscetti et al. found that median serum FGF-23 levels were signifi-

cantly higher in patients with internal carotid artery stenosis than in diabetic controls and significantly and independently associated with unstable plaque in patients with internal carotid artery stenosis [OR= 5.71 (95% CI=2.09–15.29). Hence, they concluded that FGF-23 could be associated with unstable plaques in type 2 diabetic patients with internal carotid artery stenosis [25].

Schoppet et al. investigated the association between serum FGF-23 levels, mineral metabolism parameters and abdominal aortic calcification (AAC) in males [26]. They found that FGF-23 levels decreased with age but were not associated with any other parameters before the age of 60. Also, serum FGF-23 values were correlated with age, glomerular filtration rate and PTH levels in males aged over 60 years. After adjustment for confounders, higher concentrations of C-reactive protein were also found to be associated with higher FGF-23 levels. Furthermore, subjects in the highest FGF-23 quartile had a higher prevalence of severe AAC compared with the three lower quartiles combined (OR=1.88; 95% CI=1.22–2.85; P<0.005) However, in our current study, parameters such as BMI, eGFR, CRP, ESR, creatinine, PTH, calcium, phosphate and CIMT were not associated with FGF-23 levels in AA amyloidosis patients.

Interestingly, Shah et al. found that higher FGF-23 levels were associated with greater likelihood of carotid atherosclerosis independent of CKD [27]. Therefore, they concluded that FGF-23 may affect cardiovascular events and stroke through its role in atherosclerosis. In another study performed on CKD patients, Nakayama et al. showed that FGF-23 was independently associated with carotid artery calcification (CAAC) in patients with CKD who were not on dialysis [28]. These studies support the suggestion that FGF-23 is associated with carotid plaque development and progression. However, further evidence is necessary to conclude that there is a direct cause-effect relationship between FGF23 and atherosclerosis.

Ugurlu et al showed that FMF patients had significantly higher CIMT values compared with healthy controls [14]. Also, they reported that CIMT values in FMF patients were correlated with age, BMI and fasting glucose. Similar to this study, we also found that serum FGF23 levels were associated with age but not with BMI in patients with AA amyloidosis.

Modesto et al. showed that AL amyloidosis was associated with higher CIMT values after adjustment for confounding variables [29]. In addition, Keles et al. found that the CIMT values of patients with renal amyloidosis were significantly higher than those of the normal population. In their conclusion, they stated that atherosclerosis could be accelerated in patients with amyloid-related chronic inflammation [30]. Our results are similar in terms of showing that the CIMT values of patients with AA amyloidosis are increased compared to age- and sex-matched controls.

There were certain limitations to this study. We acknowledge that the small number of AA patients in our single center study is a limitation. Additionally, although patients with other conditions that could exacerbate inflammation were excluded from the study, there are various other factors that can change the levels of inflammatory parameters. Another limitation is associated with the fact that the lifestyle and risk factors of these patients in terms of atherosclerosis were not evaluated; meaning that confounding factors may have had a role in the comparison of groups; however, patients with various chronic conditions were excluded to minimize this problem. Finally, the study is cross-sectional in design without prospective follow-up; thus a cause-effect relationship can not be drawn from our results.

CONCLUSION

AA amyloidosis patients had significantly higher CIMT values compared to the control group however

serum FGF-23 levels were similar between the groups. Serum FGF-23 levels were not associated with CIMT values in AA amyloidosis patients. Although our results suggest a lack of association between FGF-23 levels and CIMT values in patients with AA amyloidosis, we believe that further studies are required to investigate the possible role of FGF-23 in the increased atherosclerosis observed in patients with amyloidosis.

Ethics Committee Approval: Approval from the Ethics Committee of Clinical Researches of Istanbul Medeniyet University Goztepe Training and Research Hospital (2013-KAEK-64) (2018/0115 - 12.06.2018)
Conflict of Interest: The authors have no conflicts of interest to declare.
Funding: No funding was received.

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