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Evaluation of serum fibroblast growth factor-23 in patients with axial spondyloarthritis and its association with sclerostin, inflammation, and spinal damage

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Abstract

The mechanisms underlying new bone formation in individuals with axial spondyloarthritis (axSpA) remain unclear; however, low levels of sclerostin (SOST) may be associated with development of syndesmophytes in those with ankylosing spondylitis (AS). Expression of fibroblast growth factor-23 (FGF-23), another osteocyte factor, is high in those with osteoporosis and chronic renal failure, but levels in those with axSpA are unknown. To evaluate serum FGF-23 and SOST levels in axSpA patients, and to assess their relationship with inflammation and structural damage. In total, 109 axSpA patients (55 with AS and 54 with non-radiographic axSpA) and 57 healthy control (HC) subjects were included in the analysis. Serum concentrations of FGF-23 and SOST were measured and correlation analysis was performed. The presence of syndesmophytes and the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) were used to assess structural damage. Levels of serum FGF-23 in axSpA patients were significantly higher than those in HCs [median (interquartile range—IQR) FGF-23 level, pg/ml; AxSpA = 144 (82.3–253.2), HC = 107 (63.3–192.8), $p = 0.010$]; however, there was no difference in SOST levels. FGF-23 levels correlated with the erythrocyte sedimentation rate (ESR) ($r = 0.265$, $p = 0.006$) and serum C-reactive protein (CRP) level ($r = 0.229$, $p = 0.010$). In the axSpA, SOST levels correlated negatively with mSASSS ($r = -0.283$, $p = 0.007$), whereas those in the AS group correlated negatively with CRP ($r = -0.426$, $p = 0.001$). Serum FGF-23 levels were high in axSpA patients. Increased FGF-23 was associated with inflammation, but not with SOST levels or disease activity. SOST correlated negatively with both inflammation and structural damage.

Keywords Fibroblast growth factor-23 · Sclerostin · Spondyloarthritis · Ankylosing spondylitis

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Introduction

Axial spondyloarthritis (axSpA) is a chronic disease characterized predominantly by sacroiliac and spinal inflammation in addition to extra-articular manifestations. Structural damage may lead to significant morbidity, and new bone formation plays a pivotal role in this process [1]. New bone formation is driven by several mechanisms that involve cellular elements (i.e., osteocytes, and chondrocytes), cytokines, and hormones [2]. Osteocytes might regulate bone resorption and formation via secreted proteins such as sclerostin (SOST) [3]. However, the pathophysiology of new bone formation in individuals with ankylosing spondylitis (AS) is unclear. Preventing radiographic progression is one of the most attractive therapeutic goals for axSpA; therefore, it is important to recognize the underlying mechanisms [4]. The Wnt/β-catenin pathway and its inhibitors, Dikkopf-1 (DKK-1) and SOST, have been examined to assess the relationship between bone formation and pathogenesis of AS [5–7]. These studies detected impaired expression of Wnt proteins and their inhibitors, as well as decreased serum SOST and DKK-1 levels, in AS patients [5–10]. Like SOST, osteocytes secrete fibroblast growth factor-23 (FGF-23), which regulates phosphate/vitamin D (VitD) metabolism and bone turnover [3]. FGF-23 was first identified as a phosphaturic hormone [11]. FGF-23 may inhibit osteoblast differentiation and matrix mineralization, and also acts as a regulator of VitD [12]. FGF-23 has been well studied in patients with chronic kidney disease (CKD); indeed, increased levels may be an early marker for CKD-associated metabolic bone disease [13]. Recent studies show a relationship between FGF-23 and osteoporosis [14, 15]. For example, FGF-23 levels in women with postmenopausal osteoporosis and elderly men with osteoporosis are significantly higher than those in controls. In addition, FGF-23 is elevated in individuals with CKD, cardiovascular disease, and rheumatoid arthritis (RA), but the role of the FGF-23 in SpA has not been investigated [16–19]. Further investigations are needed to identify the relationship between FGF-23, disease activity, and radiographic damage in SpA.

The aim of this study was to compare serum FGF-23 and SOST levels in patients with axSpA with those in healthy controls (HCs), and to examine their relationship to inflammation and radiological damage.

Methods

Study populations

This was a cross-sectional study. Consecutive axSpA patients were recruited from the SpA cohort at a university hospital. In total, 109 axSpA patients (55 with AS and 54 with non-radiographic (nr)-axSpA) and 57 HCs were included in the analysis.

Patients were classified according to the Assessment of SpondyloArthritis International Society criteria [20]. AxSpA patients were divided into two subgroups (AS and nr-axSpA), and AS patients were classified according to the modified New York criteria [21].

The following exclusion criteria were applied: [1] age ≤ 18 years, [2] pregnant or lactating, [3] end-stage renal disease, malignant tumor, cirrhosis, hyperthyroidism, hyperparathyroidism or Cushing's syndrome, and [4] using tumor necrosis factor inhibitors (TNFi).

Ethical approval was obtained from the local ethics committee [Izmir Katip Celebi University Ethics Board, Izmir, Turkey (approval number: 27/2016)].

Data collection

Demographics (sex, date of birth, education level, smoking status, weight, height, and calculated body mass index) and disease-related characteristics were collected using a standardized questionnaire. Disease activity and function were evaluated using the Bath Ankylosing Spondylitis Disease Activity Index and the Bath Ankylosing Spondylitis Disease Functional Index, respectively. The Ankylosing Spondylitis Disease Activity Score (ASDAS) was also calculated as a measure of disease activity. The presence of syndesmophytes and the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) were used to assess structural damage.

Laboratory assay

The Westergren method was used to measure the erythrocyte sedimentation rate (ESR, mm/h), and an enzyme-linked immunosorbent assay (ELISA) was used to measure C-reactive protein (CRP, mg/L) concentrations. SOST (pg/mL) was measured using a Human SOST (Sclerostin) ELISA (Elabscience; Catalog No: E-EL-H1544) and serum FGF-23 (pg/mL) was measured using a human FGF-23 ELISA (Elabscience; Catalog No: E-EL-H1116).

Statistical analysis

Descriptive analyses were reported as the median and interquartile range [(IQR), reported as quartile 1 (Q1) and Q3] for continuous variables lacking normal distribution, and as numbers (percentages) for categorical variables. The Chi-square test or Fisher's exact test was used to analyze differences between categorical data, while the Kruskal–Wallis and Mann–Whitney *U* tests were applied to test statistical differences between continuous data. Bonferroni's correction was used for pairwise comparisons. The significance of the correlation was assessed by calculating Spearman's rank correlation coefficient.

The Statistical Package for Social Sciences software (SPSS version 15.0, SPSS Inc., Chicago, IL, USA) was used to conduct all statistical analyses. p values < 0.05 were considered significant.

Results

Baseline demographics of the study population

There was no difference between the axSpA and HC groups with respect to age and sex [median age: 38 (IQR = 31–46) vs. 36 (IQR = 30–41), $p = 0.197$; male sex: 51% vs. 44%, $p = 0.206$, respectively].

Among the axSpA subgroups, AS patients were likely to be male ($p = 0.022$), had longer disease duration ($p = 0.001$), and a higher frequency of HLA B27 ($p = 0.05$) than the nr-axSpA group. There was no difference in disease activity or functional characteristics between the AS and nr-axSpA groups (Table 1).

Table 1 Demographic and clinical characteristics of study population

	AxSpA ($n = 109$)	AS ($n = 55$)	Nr-AxSpA ($n = 54$)	HC ($n = 57$)	p*
Age (years), median (IQR)	38 (31–46)	41 (31–47)	36 (31–43)	36 (30–41)	0.197
Male sex (%)	51	61	40	44	0.206
Education duration (years), median (IQR)	11 (8–15)	11 (8–15)	11 (8–15)	N/A	–
Smoking status (ever) (%)	68.8	72.2	65.5	N/A	–
BMI, median (IQR)	25.6 (23.1–29.4)	25.5 (23.5–28.9)	26.0 (22.7–30.7)	N/A	
Disease duration (years), median (IQR)	9 (4–16)	10 (5–19)	5 (3–12)	N/A	
HLA B27 positivity (%)	54.9	65.1	45.8	N/A	
BASDAI, median (IQR)	3.7 (2.6–5.1)	3.6 (2.7–5.0)	3.8 (2.5–5.4)	N/A	
ASDAS-CRP, median (IQR)	2.5 (1.8–3.1)	2.7 (1.9–3.2)	2.3 (1.7–3.0)	N/A	
BASFI, median (IQR)	2.1 (0.72–4.5)	2.3 (0.65–4.6)	2.1 (0.77–4.2)	N/A	
BASMI, median (IQR)	2.6 (1.6–3.2)	2.8 (1.6–3.6)	2.2 (1.4–3.0)	N/A	

AS ankylosing spondylitis, *ASDAS-CRP* Ankylosing Spondylitis Disease Activity Score-C reactive protein, *axSpA* axial spondyloarthritis, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *BASMI* Bath Ankylosing Spondylitis Metrological Index, *BMI* body mass index, *HLA B27* human leucocyte antigen B27, *HC* healthy control, *IQR* interquartile range, *N/A* not available, *nr-axSpA* non-radiographic axial spondyloarthritis

*p value is between axSpA and HC

Table 2 Inflammation parameters and spinal damage findings in addition to FGF-23 and SOST level within study population

	AxSpA ($n = 109$)	AS ($n = 55$)	Nr-axSpA ($n = 54$)	HC ($n = 57$)	p*
FGF-23, median (IQR) (pg/mL)	144 (82.3–253.2)	170 (94.3–317.4)	126 (54.4–200.5)	107 (63.3–192.8)	**0.010**
SOST, median (IQR) (pg/mL)	1382 (716–1978)	1036 (413–1779)	1606 (932–2060)	1407 (1005–1818)	0.574
ESR, median (IQR) (mm/h)	17 (8–31)	23 (13–31)	11 (6–23)	10 (6–13)	**< 0.001**
CRP, median (IQR) (mg/L)	4.8 (1.75–11.1)	8.0 (2.0–20.8)	2.7 (0.7–6.5)	0.9 (0.5–2.0)	**< 0.001**
mSASSS, median (IQR)	0 (0–2)	1 (0–5)	0 (0–1)	N/A	
Presence of syndesmophyte (%)	23	35	11	N/A	

Bold p values indicate that these values are statistically significant

AS ankylosing spondylitis, *axSpA* axial spondyloarthritis, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *FGF-23* fibroblast growth factor 23, *HC* healthy control, *IQR* interquartile range, *mSASSS* modified Stoke Ankylosing Spondylitis Spinal Score, *N/A* not applicable, *nr-axSpA* non-radiographic axial spondyloarthritis, *SOST* sclerostin

*p value is between axSpA and HC

Expression of FGF-23, SOST, and inflammatory markers

Serum FGF-23 levels in axSpA patients were significantly higher than those in HCs ($p = 0.010$). Post hoc comparisons revealed that the difference was due to significantly higher FGF-23 levels in the AS group than in HCs ($p = 0.023$). Although there was a trend towards lower SOST levels in axSpA patients, the difference did not reach statistical significance (Table 2).

AxSpA patients had a higher ESR and higher CRP levels than HC (Table 2). Pairwise comparisons revealed that these differences were due to increased values in the AS group (CRP: AS vs. HC $p < 0.001$; AS vs. nr-axSpA $p < 0.001$; nr-axSpA vs. HC $p > 0.05$; ESR: AS vs. HC $p < 0.001$; AS vs. nr-axSpA $p < 0.001$; nr-axSpA vs. HC $p > 0.05$). AS patients had higher mSASSS than nr-axSpA patients.

Correlation analyses

In axSpA patients, serum FGF-23 levels correlated only with the ESR and serum CRP levels (Fig. 1). SOST levels correlated negatively with mSASSS ($r = -0.283$, $p = 0.007$). In addition, SOST levels in the AS group correlated negatively with CRP ($r = -0.426$, $p = 0.001$).

There was no significant association between bone metabolic profile markers and other disease characteristics in axSpA patients, including disease activity, symptom duration, and HLA-B27 positivity (data not given).

Discussion

Here, we evaluated expression of FGF-23 and SOST, which play roles in the bone metabolism pathway, in patients with axSpA. FGF-23 levels in patients with axSpA were significantly higher than those in HCs. This difference was due to the AS group, and was associated with expression of inflammatory markers. There was no association between SOST and FGF-23.

FGF-23 levels in patients with osteoporosis were similar to those in patients with CKD, CVD, and RA [14–19]. A previous study of RA showed that bone mineral density scores for the spine and neck in RA patients did not correlate significantly with serum FGF23 levels; however, they did show a significant and positive correlation with the ESR, CRP levels, the disease activity score-28 based on the ESR (DAS-28 ESR), and the DAS-28 CRP ($r = 0.261$, $p = 0.044$; $r = 0.280$, $p = 0.029$; $r = 0.409$, $p = 0.001$; and $r = 0.421$, $p = 0.001$, respectively) [19]. Thus, serum

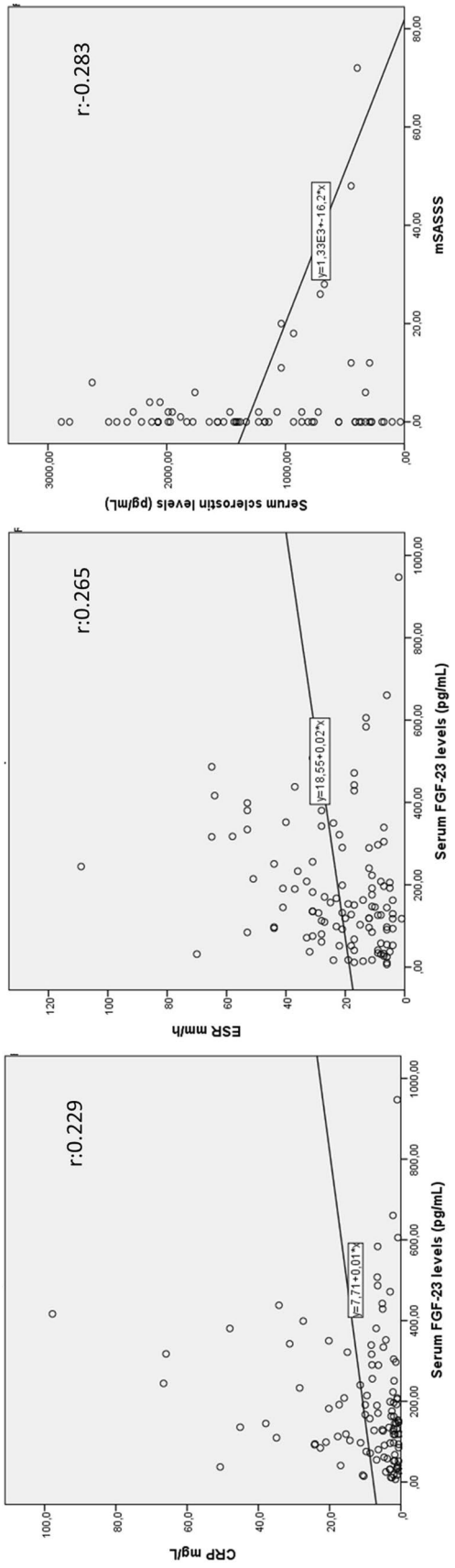

Fig. 1 Correlated factors with FGF-23 and SOST in axSpA patients. *axSpA* axial spondyloarthritis, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *FGF-23* fibroblast growth factor 23, *mSASSS* modified Stoke Ankylosing Spondylitis Spinal Score, *SOST* sclerostin

FGF23 may be associated with abnormal bone absorption related to inflammation under different conditions.

Although we observed a trend towards lower SOST levels in axSpA patients, it did not reach statistical significance. However, there was a weak correlation between SOST and mSASSS. A previous study reported that serum levels of SOST decreased in patients with AS [2, 9, 10]; however, a recent meta-analysis of seven studies found no significant difference between SOST levels in AS and HCs [22]. Discrepancies among studies may be due to different functions of SOST at different stages of bone formation [22, 23]. A previous study attempted to explain structural progression of AS in terms of cycles of bone resorption and formation [24], a process that may be associated with different SOST levels and functions at different stages of the cycle. Few studies have examined the role of SOST in axSpA, and none performed subgroup (AS vs. nr-AxSpA) analysis [25, 26]. One study reported that SOST levels in patients with axSpA were higher than those in HCs [25], whereas another reported that low levels of SOST predict development of axSpA in patients with inflammatory bowel disease [26].

Patients had the disease at different disease stages and with different activity status due to the heterogeneity of the axSpA group. In addition to that, we did not have data about the osteoporosis status of the study population.

Prospective studies of the role of FGF-23 in the pathogenesis of axSpA should be conducted to investigate different phases of the bone cycle. SOST remains an important key player in the development of new bone formation, but future studies should evaluate expression and function at different stages of disease.

In conclusion, serum FGF-23 levels in patients with axSpA, particularly those with AS, are higher than those in HCs and are associated with inflammation. SOST levels and disease activity are not. Levels of SOST, which is one of the most suitable candidate drivers of new bone formation, correlated negatively with both inflammation and structural damage.

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Compliance with ethical standards

Conflict of interest None for all authors.

Ethics approval Ethics approval was obtained from the local ethical committee [Izmir Katip Celebi University Ethics Board, Izmir, Turkey (approval number: 27/2016)]. Informed consent was obtained from all individual participants included in the study.

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