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Fibroblast growth factor 23 (Fgf23) levels and their relationship with disease activity, bone mineral density, and radiological damage score in patients with rheumatoid arthritis: a single center case–control study

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Abstract

Background: There is limited and conflicting information on Fgf23 levels and their relationship with bone loss and disease activity in rheumatoid arthritis (RA). The aim of this study was to compare Fgf23 levels in RA patients with a healthy population and to evaluate the relationship between Fgf23 levels in RA with disease activity, bone mineral density (BMD), and radiological damage score.

Results: The median Fgf23 levels in patients with RA and in hospital staff were 20.06 (11.2–51.0) and 26.40 (12.6–49.5) pg/ml ($P < 0.001$), respectively. RA patients were divided into active (DAS28 > 3.2) and inactive (DAS28 ≤ 3.2) subgroups. The median Fgf23 levels in active and inactive RA patients were 22.12 (13.90–51.02) and 17.71 (11.20–31.19) pg/ml, respectively ($P = 0.001$). BMD of RA patients was evaluated with dual-energy X-ray absorptiometry and radiological damage scores were evaluated independently by two investigators using the modified Sharp score (MSS). In RA patients, Fgf23 values correlated with DAS28 and with erosion score of observer-2 ($r = 0.297$, $P = 0.036$), but not with erosion score of observer-1 ($r = 0.252$, $P = 0.077$). No correlation was found between DAS28 and femur and lumbar vertebra BMD.

Conclusion: In RA, Fgf23 is not associated with BMD but may be associated with local bone loss and disease activity.

Keywords: Fgf23, Modified Sharp score, Bone mineral density, Rheumatoid arthritis

Background

Rheumatoid arthritis (RA) is an autoimmune disease characterized by symmetrical, inflammatory, polyarticular joint involvement of unknown etiology. Apart from joint involvement, one of the accompanying pathologies in RA is bone loss which can be seen both in general and at the affected joint level [1]. A decrease in bone mass resulting from less bone formation than the bone loss is defined as osteoporosis and its prevalence in RA patients is higher than in the normal population [2]. Osteoporosis in RA may be caused by many factors such as disease duration, systemic inflammation, or corticosteroid use [3]. Apart from the generalized bone loss, RA patients also have bone destruction and mineral loss at the affected joint level. Bone loss at joints in RA may start as bone marrow edema and progress to erosion in the marginal areas of the joint [1, 4]. The decrease in bone mineral density detected even in the early stages of RA can predict higher erosion scores [5]. Although the

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pathophysiology of bone loss in RA has not been fully elucidated, focal erosions in RA patients have been found to be associated with generalized osteoporosis, and similar mechanisms are thought to be responsible for both conditions [6–9].

Fibroblast growth factor-23 (Fgf23) is a peptide molecule produced and secreted mainly by osteocytes in bones. Fgf23 is effective in maintaining normal phosphorus levels by decreasing phosphate reabsorption from the kidneys and reducing intestinal phosphate absorption through suppression of calcitriol synthesis [10]. It has also been found that Fgf23 directly affects the parathyroid glands and reduces parathyroid hormone (PTH) synthesis [11]. Fgf23 is the earliest increasing biomarker in renal failure and is thought to be one of the hormones that cause osteoporosis in renal failure [12, 13]. Fgf23 is also associated with inflammatory cytokines such as IL-6 and TNFα, which have a role in RA pathogenesis [14]. The relationship between Fgf23 and RA has not been adequately studied so far. There are a limited number of studies in the literature evaluating Fgf23 levels in RA patients, and in these studies, conflicting results were obtained from the comparison of Fgf23 levels in RA patients compared to healthy controls, but Fgf23 levels were found to be associated with disease activity [15–17]. Sato et al. found that the serum Fgf23 levels in RA patients were positively correlated with inflammation, disease activity, and bone resorption markers [15]. In a study, serum sclerostin which may decrease bone formation was elevated in RA patients, was strongly associated with Fgf23 [17]. In another study, no significant differences in serum Fgf23 levels between RA patients and controls were found [16]. Although no relationship has been found between Fgf23 and bone mineral density (BMD) in the only report so far, its relationship with the radiological damage score is unknown [15].

The aim of this study was to evaluate the levels of Fgf23, vitamin D, calcium, phosphorus, and PTH in RA patients compared to controls, and to evaluate the relationship of Fgf23 levels with BMD, radiological damage scores in the joints, and disease activity in RA patients. To the best of our knowledge, this study is the first study evaluating the relationship between Fgf23 levels and radiological scores in RA patients and also the second study evaluating the relationship between Fgf23 and BMD besides the disease activity.

Methods

Study design and participants

The study protocol was approved by the local ethics committee (2011-KAEK-25 2018/10–18) and the study was conducted in line with the ethical rules declared in the Helsinki Declaration. Written informed consent was obtained from all participants before participating in the study. A total of 116 participants were included in this case–control study between November 2018 and August 2019, including 53 RA patients (patient group) who were followed up from the rheumatology outpatient clinic, and 53 controls (control group), including hospital staff.

Inclusion criteria

The inclusion criteria of the patient group: volunteering for study participation, being diagnosed with RA according to the 2010 ACR/EULAR criteria, not having another connective tissue disease or inflammatory arthritis, and not using chronic medications other than RA treatment [18]. The inclusion criteria for the control group: volunteering for study participation and not having any known systemic disease or current drug use.

Exclusion criteria

Exclusion criteria for all participants were as follows: being under 18 or over 75 years old, being pregnant or breastfeeding, those with glomerular filtration rate (GFR) < 60 ml/min, having cancer or diabetes mellitus or an acute infection clinically, and those receiving vitamin D replacement.

A flow chart is shown in Fig. 1 for including and excluding patients.

Assessment of the patient group

Initial evaluation

The history of all RA patients was taken to determine whether they were using current medication and whether they had a chronic disease, and general physical examinations were performed. Anti-cyclic citrullinated peptide (anti-CCP) and rheumatoid factor (RF) autoantibody results were obtained from hospital records and test results above the reference range were considered positive.

Disease activity parameters

The disease activity of patients with RA was evaluated by the disease activity score (DAS28). The joints of all patients were examined by an experienced rheumatologist, and the tender and swollen joints of 28 joints (bilaterally shoulder, elbow, wrist, knee and hand small joints) were determined. The patient global health assessment (PHA) was measured for all patients responding to the question of how they felt using a visual analog scale (VAS). The pain (VAS-pain) of the patients and the evaluator global assessment (EGA) were also evaluated using VAS. Blood samples were taken from all RA patients for the erythrocyte sedimentation rate (ESR) test. DAS28-ESR was calculated according to this formula; DAS28-ESR = (0.56*sqrt (tender joint

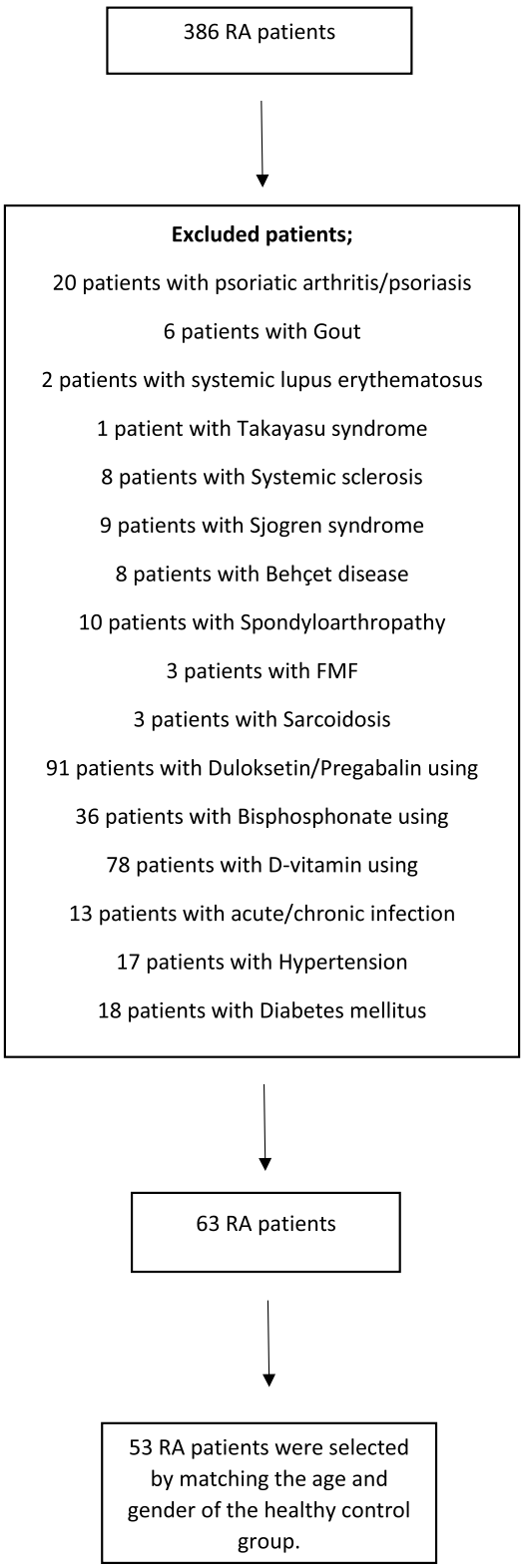

Fig. 1 The included and excluded RA patients

count)) + (0.28*sqrt(swollen joint count)) + (0.7*ln(ESR)) + (0.014*PHA).

Measurement of bone mineral density (BMD)

Bone mineral density measurement was evaluated by the dual-energy X-ray absorptiometry (DEXA) method. A Hologic QDR 4500 A DEXA (Hologic INC 02,154, USA) device was used. Total values measured as gr/cm^2 were taken into consideration when evaluating vertebra BMD and femur BMD. A *T*-score of − 2.5 or lower values in DEXA was defined as osteoporosis.

Evaluation of radiological damage

Anteroposterior X-rays of both hands and both feet were taken and placed on the same film for all RA patients. The X-ray tube was placed 100 cm from the cassette and the third metacarpophalangeal (MCP) joint for the hand and the third metatarsophalangial (MTP) joint for the foot were positioned in the center while X-ray films were taken. Based on the X-ray images of RA patients, radiological damage of the joints was evaluated using the modified Sharp score (MSS), a scoring system in which narrowing of joint space and erosion of the joints are evaluated by grading [19, 20]. With this scoring method, joints of hands and feet were scored separately.

Evaluation of hand joints Evaluation of erosion on the surfaces of hand joints were made for a total of 16 joints. These joints were: interphalangeal joint of the thumb, 2–5 proximal interphalangeal (PIP) joints, 1–5 MCP joints, trapezo-metacarpal joint of the thumb, and joints of the trapezius, scaphoid, lunate, radius, and distal ulna. The erosion score per joint of the hands ranged from 0 to 5. If the erosion was clearly visible, 1 point was given. 2 points if more than 25% of the surface area of the relevant joint was affected, 3 if more than 50% was affected, and 4 points if more than 75% was affected. If the joint collapsed completely or the entire surface of the joint was affected, 5 points were given. A maximum of 80 erosion points were scored for one hand. Scoring of each hand was done separately. When evaluating the joint space, a total of 15 joints were examined. These were carpometacarpal 3–4-5, MCP 1–5, PIP2-5, scaphoido-capitate, scaphoido-radial, and scaphoido-trapezium joints. Each joint was scored from 0 to 4. A normal joint space was scored as 0 and in the presence of focal stenosis, 1 point was given. In the presence of diffuse stenosis, 2 points were given if the stenosis was less than 50% of the joint space, and 3 points were given if it was more. In addition, the joint subluxation also scored 3 points. Complete

ankylosis or luxation of the joint was scored as 4. Thus, the maximum joint space score for each hand was 60.

Evaluation of the foot joints Evaluation of MSS in the foot was performed for a total of 6 joints. These joints were the interphalangial joint of the first toe and the 1–5 MTP joints. The scoring criteria were the same as for the hands. The only difference was that the erosion score of the foot was evaluated for each joint for 2 surfaces (proximal and distal). Thus, the maximum erosion score per foot was 60 and the maximum joint space narrowing score per foot was 24.

Observers MSS for all RA patients were evaluated independently by two experienced rheumatologists, and afterwards, the erosion and joint space narrowing scores for both hands and feet were evaluated separately by each observer; all scores were summed and the total MSS was calculated for each observer.

Assessment of the control group

All control group participants were questioned about the drugs they used and their chronic diseases, general physical examinations were performed, and laboratory results in hospital records and prescriptions in the electronic archive were examined. Those who met the study criteria were included in the study.

Laboratory tests

Five milliliter of venous blood was obtained after 8 h of fasting in the morning. Fgf-23 was measured in duplicate using a standard ELISA kit (Elabscience®, Houston/TX, US). Serum calcium, phosphorus, albumin, creatinine, parathyroid hormone, and 25-hydroxyvitamin D levels were measured with commercially available kits. Corrected calcium was calculated according to this formula: corrected calcium = serum calcium + 0.8 * (4 − patient albumin). Glomerular filtration rate (GFR) was also calculated according to the formula: GFR = 186 * ([serum creatinine]$^{-1.154}$) * ([age]$^{-0.203}$) * (0.742 if female).

Comparisons between groups and subgroups

Among the RA patients, those with a DAS28 score of 3.2 and below were included in the inactive RA subgroup, and those with a DAS28 score above 3.2 were included in the active RA subgroup. While demographic data and laboratory findings were compared between groups and subgroups, the frequency of drugs used by RA patients, presence of autoantibodies, disease duration, disease activity parameters, BMD values, and MSSs were also compared between the subgroups.

Statistical analysis

Analysis of the data was performed using the IBM SPSS 22.0 statistics package program. The data was previously subjected to a normal distribution analysis with Kolmogorov-Smirnow or Shapiro–Wilk tests. Student's *t*-test was used for the comparison between the two groups for continuous variables with normal distribution, and the Mann–Whitney *U* test was used for continuous variables without normal distribution. Inter-observer reliability was expressed by Kappa statistics. Reliability was determined by intra-class correlation coefficients (ICC). Interpretation of the correlations was: 0–0.20 slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good and 0.81–1.00 excellent. Pearson's chi-square (χ^2) or chi-square (χ^2) test was used for the comparison of categorical data. Spearman's correlation analysis was used for correlation analysis. *P* value ≤ 0.05 was considered statistically significant.

Results

Patient group and controls

Comparison of demographic data and laboratory findings of RA patients and controls is shown in Table 1. Age and gender were not different between RA patients and controls ($P = 0.897$, $P = 0.659$, respectively). Mean corrected plasma calcium levels in RA patients and controls were 9.20 ± 0.40 and 8.80 ± 0.40 mg/dl, ($P < 0.001$), while mean plasma phosphorus levels were 3.0 ± 0.60

Table 1 Comparison of demographic data and laboratory findings in rheumatoid arthritis patients and controls

	RA patients (*n* = 53)	Controls (*n* = 53)	*P*
Age, years, median (min–max)	45.00 (26–73)	45.00 (29–68)	0.897
Female, *n* (%)	38 (71.7)	40 (75.50)	0.659
Postmenaposal, *n* (%)	16 (42.1)	16 (40.0)	0.850
Laboratory			
Biochemical, mean ± SD			
Corrected calcium, mg/dl	9.2 ± 0.4	8.8 ± 0.4	< 0.001*
Phosphorus, mg/dl	3.0 ± 0.6	3.5 ± 0.6	< 0.001*
GFR, ml/minute	101.8 ± 21.2	104.2 ± 23.0	0.576
Hormonal, median (min–max)			
25-hydroxyvitamin D, ng/ml	10.0 (3.0–40.0)	16.0 (5.0–29.7)	0.002*
PTH, pg/ml	67.0 (16–474)	34.4 (16–89)	< 0.001*
FGF23, pg/ml	20.6 (11.2–51.0)	26.4 (12.6–49.5)	< 0.001*

RA Rheumatoid arthritis, *min* Minimum, *max* Maximum, *SD* Standard deviation, *GFR* Glomerular filtration rate, *PTH* Parathyroid hormone, *FGF23* Fibroblast growth factor23

* $P \leq 0.05$

and 3.50 ± 0.60 mg/dl, respectively ($P < 0.001$). GFRs were not different between groups ($P = 0.576$). In RA patients and controls, the median 25-hydroxyvitamin D levels were 10.00 (3–40) and 16.00 (5–29.7) ng/ml ($P = 0.002$), median PTH levels were 67.00 (16–474) and 34.40 (16–89) pg/ml ($P < 0.001$), and median Fgf23 levels were 20.06 (11.2–51.0) and 26.40 (12.6–49.5) pg/ml ($P < 0.001$), respectively.

Analyses in the patient group

Inter-observer compatibility

Inter-observer compatibility assessed by ICC was good to excellent. ICC was 0.999 for total MSS, total erosion score, and hand and foot total erosion scores, 0.998 for total joint space narrowing score, and 0.997 for hand and foot total joint space narrowing scores.

Active and inactive subgroups

Demographic data, autoantibodies, disease activity parameters, medications, bone mineral density, and modified Sharp scores for active and inactive rheumatoid arthritis patients are shown in Table 2. Age, gender, disease duration, and autoantibody positivity were not different between active and inactive RA subgroups. All activity parameters including DAS28 values, number of tender joints and swollen joints, PGHA, EGA, VAS-pain and ESR values were different between subgroups ($P < 0.001$). Twenty-three (79.3%) of the active RA patients and 13 (54.2%) of the inactive RA patients were using glucocorticoids ($P = 0.051$). Drug use was not different between subgroups. Total femur and lumbar vertebra bone mineral density measured in gr/cm^2 and total MSSs evaluated separately by the two observers were not different between RA subgroups. Comparison of laboratory results for active and inactive RA patients is shown in Table 3. Mean values of corrected plasma calcium, phosphorus levels, and GFRs were not different between active and inactive RA patients. The median levels of Fgf23 in the active and inactive RA subgroups were 22.12 (13.90–51.02) and 17.71 (11.20–31.19) pg/ml, respectively ($P = 0.001$). The median 25 hydroxyvitamin D and PTH levels were not different between RA subgroups.

Table 2 Comparison of demographic data, autoantibodies, disease activity parameters, medications, bone mineral density, and modified Sharp scores in active and inactive rheumatoid arthritis patients

	RA patients		*P*
	DAS28 > 3.2 (*n* = 29)	**DAS28 ≤ 3,2 (*n* = 24)**	
Age, years, median (min–max)	47 (26–65)	43 (29–73)	
Female, *n* (%)	23 (79.3)	15 (62.5)	0.176
Postmenaposal, *n* (%)	12 (52.2)	4 (26.7)	0.120
DD, months, median (min–max)	72 (4–400)	42.0 (3–216)	0.102
RF, positive, *n* (%)	19 (65.5)	16 (66.7)	0.930
CCP, positive, *n* (%)	18 (62.1)	20 (83.3)	0.087
DAP, median (min–max)			
DAS28	4.9 (3.3–6.4)	2.5 (1.4–3.2)	< 0.001
Tender joint count	3 (0–11)	0 (0–2)	< 0.001
Swollen joint count	2 (0–11)	0 (0–3)	< 0.001
PHA	50 (0–100)	10 (0–33)	< 0.001
EGA	45 (10–90)	10 (0–27)	< 0.001
VAS-pain	40 (0–90)	10 (0–30)	< 0.001
ESR, mm/h	38 (12–76)	17.5 (3–51)	< 0.001
Medication, n (%)			
Methotrexate	12 (41.4)	10 (41.7)	0.983
Hydroxychloroquine	15 (53.6)	13 (46.4)	0.859
Leflunomide	12 (41.4)	12 (52.0)	0.530
Sulfasalazine	3 (10.3)	3 (12.5)	> 0.99
Glucocorticoids	23 (79.3)	13 (54.2)	0.051
Anti-TNFα	5 (17.2)	2 (8.3)	0.340
Tofacitinib	2 (6.9)	2 (8.3)	> 0.99
Tocilizumab	1 (3.4)	1 (4.2)	> 0.99
Rituximab	1 (3.4)	0 (0)	> 0.99
BMD, gr/cm^2, mean ± SD			
Femur	0.9 ± 0.1	0.9 ± 0.1	0.809
Lombar vertebra	0.9 ± 0.2	0.9 ± 0.2	0.586
Modified Sharp total score, median (min–max)			
Observer-1	27 (0–220)	20 (0–64)	0.136
Observer-2	26 (0–218)	21 (0–65)	0.129

RA Rheumatoid arthritis, *DAS28* Disease activity score-28 joints, *min* Minimum, max Maximum, *DD* Disease duration, *RF* Rheumatoid factor, *CCP* Cyclic citrulinated peptide, *DAP* Disease activity parameters, *PHA* Patient global health assessment, *EGA* Evaluator global assessment, *VAS* Visual analog scale, *ESR* Erythrocyte sedimentation rate, *TNF-α* Tumor necrosis factor α, *BMD* Bone mineral density, *SD* Standard deviation

* $P \leq 0.05$

Possible confounding factors

Medication

P values showing the difference in Fgf23, vitamin D, calcium, phosphorus, and parathyroid hormone levels in patients with rheumatoid arthritis according to drug use are shown in Table 4. Plasma Fgf23, calcium, phosphorus, parathyroid hormone, and 25 hydroxyvitamin D levels were not different among RA patients whether any drug was used or not ($P > 0.05$).

Correlation of Fgf232 with other laboratory data

Plasma Fgf23 levels in RA patients did not correlate with corrected plasma calcium ($r = -0.106$, $P = 0.449$),

Table 3 Comparison of laboratory results for active and inactive rheumatoid arthritis patients

	RA patients		*P*
	DAS28 > 3.2 (*n* = 29)	**DAS28 ≤ 3,2 (*n* = 24)**	
Biochemical, mean ± SD			
Corrected calcium, mg/dl	9.2 ± 0.36	9.2 ± 0.35	0.959
Phosphorus, mg/dl	3.1 ± 0.54	2.9 ± 0.67	0.278
GFR, ml/min	100.7 ± 20.31	103.1 ± 22.61	0.688
Hormonal, median (min–max)			
25-hydroxyvitamin D, ng/ml	10 (4–40)	9.5 (3–34)	0.872
PTH, pg/ml	67 (24–474)	66 (16–172)	0.586
Fgf23, pg/ml	22.12 (13.90–51.02)	17.71 (11.20–31.19)	0.001*

RA Rheumatoid arthritis, *DAS28* Disease activity score-28 joints, *SD* Standard deviation, *GFR* Glomerular filtration rate, *min* Minimum, *max* Maximum, *PTH* Parathyroid hormone, *Fgf23* Fibroblast growth factor 23

* $P \leq 0.05$

Table 4 *P* values showing differences in fibroblast growth factor-23, 25-hydroxyvitamin D, calcium, phosphorus, and parathyroid hormone levels in patients with rheumatoid arthritis according to drug use

	Fgf23	25-hydroxy vitamin D	Calcium	Phosphorus	PTH
Glucocorticoids	0.682	0.939	0.871	0.359	0.109
Methotrexate	0.752	0.921	0.580	0.978	0.348
Hydroxychloroquine	0.581	0.509	0.480	0.199	0.219
Leflunomide	0.357	0.421	0.767	0.204	0.532
Sulfasalazine	0.288	0.837	0.169	0.593	0.178
Anti-TNF	0.807	0.478	0.332	0.462	0.969
Other biological drugs[a]	0.969	0.478	0.126	0.319	0.690

Fgf23 Fibroblast growth factor 23, *PTH* Parathyroid hormone, *TNF-α* Tumor necrosis factor alfa

[a] Tofacitinib, tocilizumab, and rituximab

phosphorus ($r = 0.187$, $P = 0.181$), PTH ($r = -0.121$, $P = 0.389$), or 25 hydroxy vitamin D levels ($r = 0.210$, $P = 0.131$).

Association of Fgf23 levels with BMD, MSS, disease duration, and disease activity

Correlations of Fgf23 with modified Sharp score, bone mineral density, disease duration, and disease activity in RA patients are shown in Table 5. A significant correlation was found between the erosion score of Observer-2 and Fgf23 ($P = 0.036$). The correlation between the erosion score of Observer-1 and Fgf23 level was close to being significant ($r = 0.252$, $P = 0.077$). Observer-1 and Observer-2's joint spacing

Table 5 Correlations of fgf23 with modified Sharp score, bone mineral density, disease duration, and disease activity in RA patients

	Fgf23	
	r	***P***
Modified Sharp score		
Observer-1		
Total score	0.202	0.159
Erosion score	0.252	0.077
Hand	0.266	0.062
Foot	0.186	0.197
Joint space narrowing	0.228	0.112
Hand	0.248	0.082
Foot	0.150	0.300
Observer-2	0.210	0.144
Total score	0.241	0.092
Erosion score	0.297	0.036
Hand	0.165	0.254
Foot	0.232	0.105
Joint space narrowing	0.260	0.069
Hand	0.149	0.302
Foot	0.202	0.159
BMD, gr/cm²		
Femur	− 0.005	0.972
Lumbar	− 0.058	0.681
Disease duration, months	0.094	0.505
Disease activity		
DAS28	0.333	0.015
ESR, mm/saat	0.316	0.021

Fgf23 Fibroblast growth factor 23, *p* Correlation coefficient, *BMD* Bone mineral density, *DAS28* Disease activity score-28 joints, *ESR* Erythrocyte sedimentation rate

* $P \leq 0.05$

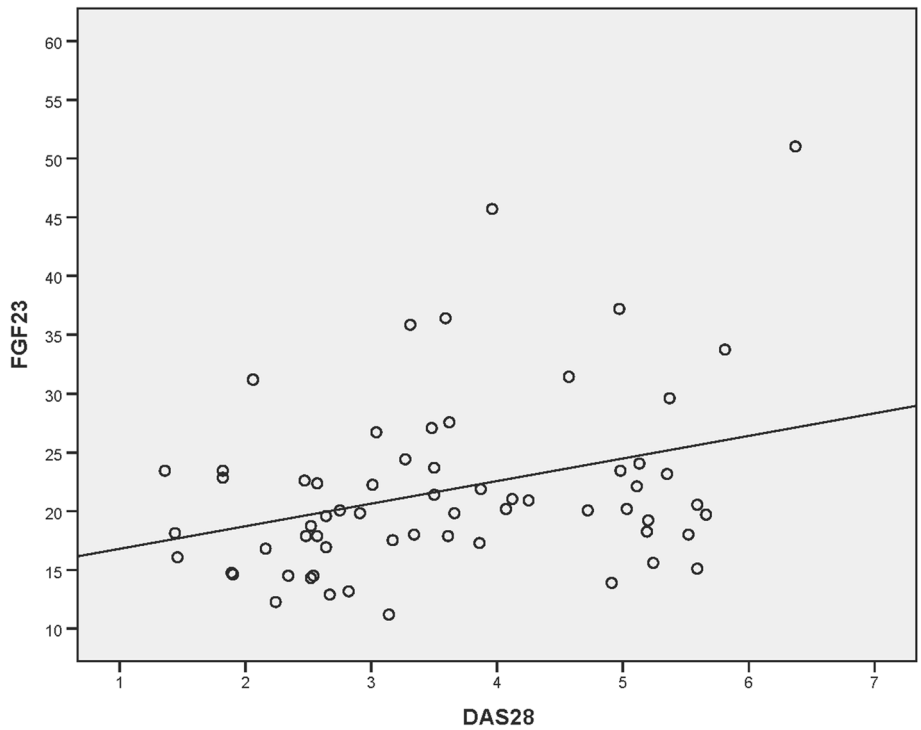

Fig. 2 Scatter plot showing the correlation between DAS28 and Fgf23. DAS28, disease activity score 28; Fgf23, fibroblast growth factor 23. There is a weak correlation between DAS28 and Fgf23 levels

narrowing scores were not significantly correlated with Fgf23 levels in either the hand or the foot. There was no correlation between the femur and lumbar vertebra BMD values and Fgf23 levels. There was also no significant correlation between RA disease duration and Fgf23 levels. When the correlation between disease activity and Fgf23 levels was evaluated, it was seen that both DAS28 ($r=0.333$, $P=0.015$) and ESR ($r=0.316$, $P=0.021$) were correlated with Fgf23 levels. The scatter plot showing the correlation between DAS28 and Fgf23 is shown in Fig. 2.

Discussion

In this study, Fgf23 levels were found to be lower in RA patients compared to controls that did not differ in terms of age, gender, and renal functions. A strong positive correlation was found between disease activity and Fgf23 levels in RA patients. When the relationship between bone loss and Fgf23 levels was evaluated, a weak relationship was detected with the radiological erosion score, while no relationship was found with bone mineral density. There is very limited information about Fgf23 levels in RA patients in the literature, and the data are conflicting. Alvarez-Cienfuegos et al. found that Fgf23 levels in RA patients were not different from controls, while klotho level, which is the co-receptor for Fgf23, was found to be higher than controls [16]. However, Fayed et al. found higher Fgf23 levels in RA patients compared to controls [17]. When the results of this study are evaluated together with the results of other studies in which Fgf23 levels have been investigated in RA patients so far, Fgf23 levels may not be constant in RA patients and may be affected by other factors. One of these factors may be vitamin-D supplementation. There are many studies indicating that vitamin D replacement increases Fgf23 levels in individuals with vitamin D deficiency [21, 22]. The reason why Fgf23 levels were found to be high in RA patients in the study of Fayed et al. may be that more than half of the patients in their study were taking vitamin-D supplements in prophylactic doses [17]. In the current study, patients undergoing vitamin-D supplementation were not included, so we think that the results of the present study reflect the Fgf23 levels in RA patients more objectively. In fact, the results of the studies comparing the levels of Fgf23 in connective tissue diseases other than RA compared to controls are not very different from the results of the present study. Kotyla et al. found lower Fgf23 levels in patients with systemic sclerosis than in controls, and in another study, Fgf23 levels were not different in SLE patients not using cyclosporine compared to controls [23, 24].

Fgf23 has direct effects on calcium-phosphorus metabolism by reducing phosphorus reabsorption in the proximal tubule as well as indirect effects by reducing active vitamin D production and by inhibitory effects on PTH [25].One of the ways to objectively evaluate the effect of Fgf23 on calcium-phosphorus metabolism is to evaluate laboratory findings in cases with tumor-induced Fgf23 elevation in the presence and absence of the tumor. Kumar et al. reported a case with a Fgf23 secreting mesenchymal tumor in which hypophosphatemia, high renal tubular phosphate excretion and severe osteoporosis were observed in the preoperative period and in which all findings were completely resolved in the postoperative period [26]. There are other cancer patients reported in the literature who had hypophosphatemia, phosphaturia, and increased Fgf23 levels in the preoperative period and whose findings improved after tumor excision [27, 28]. Ultimately, although the net effect of Fgf23 appears to cause osteoporosis by accelerating the loss of phosphorus, its effects are complex in inflammatory diseases accompanied by osteoporosis, as Fgf23 is also associated with inflammation. Studies so far have shown a consistent relationship between Fgf23 and chronic kidney disease (CKD) that is commonly accompanied by chronic inflammation, such that plasma Fgf23 levels begin to rise with mild kidney damage and continue to increase as kidney failure progresses [12, 29]. However, the relationship between Fgf23 and osteoporosis in CKD is contradictory. Urena Torres et al. found that there was no relationship between Fgf23 and bone mass in hemodialysis patients [30]. Coskun et al. also found that there was no relationship between Fgf23 and bone mass in post-transplant patients [31]. However, Desbiens et al. reported that in hemodialysis patients, those with high Fgf23 levels had a higher fracture risk and Slouma et al. also found Fgf23 levels to be higher in hemodialysis patients with lumbar osteoporosis [32]. In a study evaluating the relationship between Fgf23 and inflammatory bowel diseases (IBD), Fgf23 levels were found to be higher than controls, and in addition, BMD levels were found to be lower and Fgf23 levels to be higher during IBD exacerbations compared to the state in remission [33]. Although Fgf23 has been shown to predict adverse cardiovascular outcomes in diabetic patients with coronary heart disease, Fgf23 levels were generally not different between diabetic and non-diabetic patients [34]. However, when the relationship between Fgf23 and osteoporosis was evaluated in patients with type 2 DM, it was found that Fgf23 levels were lower in type 2 DM patients with osteoporosis than those without, and Fgf23 was positively correlated with bone mineral density in type 2 DM patients [35]. Fgf23 may have a role in the etiology of osteoporosis accompanying IBD, but its effect on osteoporosis in CKD is complex and appears to be unrelated to osteoporosis in type 2 DM. RA also exhibits chronic inflammation and osteoporosis is often present. However, considering that Fgf23 levels in RA patients were lower than controls and Fgf23 was not correlated with bone mineral density in the current study, it suggests that Fgf23 may not have a role in the etiopathogenesis of osteoporosis in RA. Indeed, in the only study conducted on this subject, Sato et al. did not find a relationship between Fgf23 levels and lumbar or femoral bone mineral density in RA patients [15].

There are many studies in the literature showing that Fgf23 is associated with inflammation, and Sato et al. also found Fgf23 levels to be highly correlated with disease activity in RA patients [15, 36, 37]. In this study, a strong positive relationship was found between Fgf23 and disease activity, in accordance with the literature data. Moreover, when the relationship between Fgf23 and radiological erosion was evaluated, a significant relationship was also found between the erosion score of the hand joints and Fgf23. Since the Sharp erosion score is highly correlated with bone mineral density of involved joints, the correlation between the erosion score and Fgf23 levels may also suggest a relationship with Fgf23 and local bone resorption [38]. Guler-Yuksel et al. showed that bone loss in the hand started earlier than a generalized bone loss in a 2-year follow-up of newly diagnosed RA patients. And in another study, it has been shown that hand bone loss can occur even in the preclinical period of RA [39]. The reason that Fgf23 is not associated with generalized osteoporosis but is associated with the joint erosion score may be due to the fact that the erosion score indicates bone loss more accurately especially in early-stage patients or because of the difference in local and systemic effects of Fgf23 on the bones. There is not enough literature data on this subject and further research is needed to clarify the issue. Considering the correlation of Fgf23 with disease activity and erosion score as well as its physiological effects, controlling disease activity may also contribute to the prevention of local bone loss via Fgf23.

Limitations

In this study, we attempted to evaluate local bone loss based on the radiological damage score of the joints. The local bone density of the joints affected by RA was not evaluated quantitatively by DEXA or similar methods is one of the limitations of the study. The control group participants included in this study consisted of hospital staff so they did not adequately represent the healthy population is another important deficiency of the study. Another limitation of the study is that generalized

osteoporosis was evaluated only with DEXA and not evaluated together with bone formation and resorption markers.

Conclusion

In summary, fgf23 levels were lower in RA patients compared to controls, while Fgf23 was not associated with generalized bone loss, but may have been associated with local bone loss and disease activity in RA patients. Inflammation may affect the serum Fgf23 levels in RA and it may be used as an inflammation and disease activity marker in RA patients. Further research is needed to reveal the relationship between inflammation, disease activity, and Fgf23 levels in RA.

Abbreviations

Fgf23: Fibroblast growth factor 23; RA: Rheumatoid arthritis; BMD: Bone mineral density; GFR: Glomerular filtration rate; MSS: Modified Sharp score; Anti-CCP: Anti-cyclic citrullinated peptide; RF: Rheumatoid factor; PHA: Patient global health assessment; VAS: Visual analog score; EGA: Evaluator global assessment; ESR: Erythrocyte sedimentation rate; DEXA: Dual-energy X-ray absorptiometry; MTP: Metatarsophalangial; MCP: Metacarpophalangeal; PIP: Proximal interphalangeal; ICC: Intra-class correlation coefficients; PTH: Parathyroid hormone; CKD: Chronic kidney disease; IBD: Inflammatory bowel diseases.

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Authors' contributions

Study concept and design: KA; Study concept and design: DŞÇ; Analysis and interpretation of data: KA, SE, DŞÇ; Drafting of the manuscript: KA, SE, DŞÇ; Assessment of Plasma Fibroblast growth factor 23 level: YÜ; All authors have read and approved the manuscript.

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Availability of data and materials

The data will be available upon request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the local ethics committee (2011-KAEK-25 2018/10–18) and the study was conducted in line with the ethical rules declared in the Helsinki Declaration. Written informed consent was obtained from all participants before participating in the study.

Consent for publication

All parents of the participants accepted the publication of this research.

Competing interests

The authors declare that they have no known competing interests or personal relationships that could have appeared to influence the work reported in this paper.

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