C-telopeptide of type I collagen (CTX-1) in premenopausal Egyptian women with fibromyalgia syndrome

Shereen M. Olama[a,c], Tamer O. ElSaid[a], Mohammad M. El-Arman[b]

Departments of [1]Rheumatology and Rehabilitation, [2]Clinical Pathology, Faculty of Medicine, Mansoura University, Mansoura, Egypt, [3]Department of Rheumatology, Faculty of Medicine, Northern Border University, Arar, Saudi Arabia

Correspondence to Shereen Mohamed Olama, MD, Department of Rheumatology and Rehabilitation, Faculty of Medicine, Mansoura University, Mansoura, Egypt
Tel: +20 502 366 942; 0020101954652;
e-mail: olamasm@yahoo.com

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Introduction
The majority of the fibromyalgia syndrome (FMS) patients do not exercise regularly and their physical fitness is low. Physical inactivity accelerates bone loss. This suggests that FMS patients are at risk in terms of osteoporosis. The aim of this study was to measure serum C-telopeptide of type I collagen (CTX-1) as a marker of bone resorption in premenopausal women with FMS.

Patients and methods
A total of 100 premenopausal female patients with FMS diagnosed according to the American College of Rheumatology (ACR) criteria 1990 and 50 healthy women were chosen to serve as the control group. Serum CTX-1 levels were measured using beta-CrossLaps Roche Elecsys.

Results
The serum CTX-1 level was significantly higher in patients with FMS compared with the control group. The mean serum CTX-1 in FMS patients was 340.2 ± 112.6 pg/ml compared with 283.6 ± 113.1 pg/ml in controls ($P = 0.004$). The serum CTX-1 level was positively correlated with the visual analogue scale(VAS) of pain ($P = 0.028$), the VAS of fatigue ($P = 0.031$), the VAS of global severity ($P = 0.016$), the VAS of anxiety ($P = 0.013$), the Health Assessment Questionnaire score ($P = 0.022$), the Fibromyalgia Impact Questionnaire ($P = 0.010$), the Beck Depression Inventory ($P = 0.007$), the tender points count ($P = 0.003$), the tender points score ($P = 0.004$), and the Pittsburg Sleep Quality Index ($P = 0.021$). The mean serum CTX-1 level was also significantly higher in FMS patients with postexertion pain ($P = 0.010$), confusion ($P = 0.025$), dizziness ($P = 0.012$), depression ($P = 0.029$), mood disturbance ($P = 0.018$), anxiety ($P = 0.030$), short memory difficulties ($P = 0.017$), and sleep disturbance ($P = 0.028$) than in those without these symptoms.

Conclusion
We found a significant increase in serum CTX-1 in FMS patients compared with controls, and this was correlated with the disease severity. Increased CTX-1 may lead to the early development of osteoporosis. More comprehensive and detailed studies are needed to determine the exact role of CTX-1 in FMS.

Keywords:
C-telopeptide of type I collagen, fibromyalgia, osteoporosis

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Introduction

Fibromyalgia syndrome (FMS) is a nonarticular rheumatic disorder characterized by widespread musculoskeletal pain, an uncertain etiology, increased tenderness in multiple points, sleep disturbances, a decreased pain threshold, and several symptoms including fatigue. FMS is common in the age group of 30–60 years. In all, 85–90% of the patients are women [1].

Regular exercise certainly plays a primary role in protection against osteoporosis [2]. The majority of the FMS patients do not exercise regularly and their physical fitness is low. Physical inactivity accelerates bone loss. This suggests that FMS patients are at risk in terms of osteoporosis.

Several studies have investigated the possible pathophysiology of osteoporosis in psychiatric patients and have hypothesized a link between depression and a low bone mineral density (BMD) [3].

Dual X-ray absorptiometry (DXA) is the gold standard for the diagnosis of osteoporosis [4]. Some conditions such as osteoarthritis, osteomalacia, overlying metal objects, vascular calcification near the spine, and previous fracture of the hip, the spine, and the wrist, and severe scoliosis can interfere with BMD interpretation [5]. Evaluating the quality of bone mineral tissue is necessary to estimate the efficacy of treatment. Bone markers indicating the bone turnover and remodeling are used for assessing the quality of bone tissue. Bone turnover controls calcium homeostasis and the replacement of parts of the bone with microfractures [6]. During these processes, several products of bone resorption and formation release into the circulation, and measuring their concentrations could estimate the rate of bone turnover.

Bone resorption markers include urinary hydroxyproline, urinary deoxypyridinoline, urinary pyridinoline, collagen type I cross-linked N-telopeptide (NTx), and collagen type I cross-linked C telopeptide (CTX-1) [7,8]. Bone biomarker could indicate the efficacy of early treatment before changes in BMD are presented [5].

BMD by DXA for this purpose is a reliable marker, but this test cannot measure the bone turnover. Moreover, DXA is not suitable for tracking the treatment over a short-term period. Also, the decrease in the fracture frequency due to therapy is much greater than that justified by the increase in the bone density. Therefore, bone biomarkers have propounded for the early detection of the efficacy of treatment [9].

Traditional biochemical markers of bone turnover such as alkaline phosphates play a valuable role in assessing bone formation and mineralization, but are not specific to the bone tissue. Recently, the value of new biomarkers such as CTX-1 were explained for predicting the bone turnover during the course of treatment [10].

The aim of this study was to measure serum CTX-1 as a marker of bone resorption in premenopausal women with FMS.

Patients and methods

This was a cross-sectional case–control descriptive study that was carried out between May and September 2013 at the outpatient clinic of the Department of Rheumatology and Rehabilitation at Mansoura University Hospital, Egypt. A total of 100 female patients with primary FMS were recruited. The diagnosis of fibromyalgia was made according to the American College of Rheumatology criteria [1,11].

All FMS patients were premenopausal to eliminate the effect of menopause on bone alteration (turnover); their ages ranged from 26 to 48 years.

Exclusion criteria

Patients were excluded from the study if they had a previous treatment with prednisone or other medication interfering with bone metabolism such as estrogen or progesterone, contraceptive therapy, bisphosphonates, and calcitonin.

Pregnant women and patients having diabetes mellitus, hypertension, unstable medical or psychiatric illness, psychosis, bone disorders, or other medical conditions such as hyperthyroidism, hyperparathyroidism, previous malignancy, renal diseases, or any systemic disease other than FMS were excluded from the study. None of our patients were smokers.

Whole body physical examination and further investigations for suspected patients were conducted.

None of our patients were taking medications other than analgesics and NSAIDs. None of our patients were on physical therapy or any other form of treatments.

About 50 healthy women among the hospital staff and some of their relatives who were age matched to the patients were chosen to serve as the control group. They were all free of psychotropic medication and had no history of psychiatric disorders.

Written consent was obtained from each eligible participant in this study after approval of this study from the local Ethical Committee.

Clinical assessment

Eligible participants completed preliminary questionnaires inquiring into demographic characteristics, the medical history, and the history of receiving any medication, and then underwent a thorough clinical examination. Pain, fatigue, anxiety, and the global severity of illness were assessed using the visual analogue scale (VAS) (0–100 mm, with higher scores indicating more pain) [12]. The18 tender points (TPs) of FMS were evaluated by palpation with the pulp of the thumb at a pressure enough to blanch a thumbnail. The following scoring system for the grading the severity of TPs was used: 0 = no pain; 1 = mild (complaint of pain without grimace); 2 = moderate (pain plus grimace); 3 = severe (pain plus marked flinch or withdrawal); and 4 = unbearable (patient is 'untouchable', withdraws without palpation) [1].

The clinical severity or the current health status of the FMS was evaluated using the Fibromyalgia Impact Questionnaire (FIQ); a self-reported instrument consists of 10 items (physical impairment, feel good, work missed, interference with performing their job, pain, fatigue, morning tiredness, stiffness, anxiety, and depression). Each item was standardized on a scale ranging from 0 to 10 (with 10 indicating greater impairment). A high total value (maximum 100) indicates severe effects on daily activities [13]. Health-related quality of life was assessed using the global self-rating index (GSI). GSI is a self-administrated instrument that covers three parts considered to be important to patients with disorders of the locomotor system: physical condition, psychological condition, and sleep disturbances. The sum of the items results in a total 0–10 score, where 10 represents the highest measured degree of health-related quality of life [14]. Functional

assessment or ability was measured using the Stanford Health Assessment Questionnaire (HAQ), which covers nine general component categories (dressing and grooming, arising, eating, walking, hygiene, reach, grip, outside activity, and sexual activity) [15].

Sleep problem was assessed according to the Pittsburg Sleep Quality Index (PSQI). PSQI is a self- reported tool to assess the quality and patterns of sleep over the last month. The PSQI measures seven subscales: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping pills, and daytime. Each subscale is rated from 0 (not in the past month) to 3 points (three or more times per week). A global sleep quality score is then obtained by summing the seven components (ranges from 0 to 21). A PSQI total score of at least 5 indicates poor sleep quality [16].

The presence of depression was evaluated using the Beck Depression Inventory-II, a 21-item self-reported questionnaire assessing both the presence and the severity of depression. The scores of each item range between 0 and 3 (0 = least, 3 = most). A total score that ranges from 0 to 63 with a cutoff point of 18 [17].

Laboratory assessment

Serum CTX-1 was determined by beta-CrossLaps Roche Elecsys (ECLIA; Roche Diagnostics, Mannheim, Germany). The sensitivity of the assay was 0.01 ng/ml.

Serum CTX-1 is influenced by renal function; it also shows significant diurnal variability with a peak in the early morning and a nadir in the afternoon, and food intake leads to a decrease in the level. Therefore, sample collection needs to be standardized, and performed in a fasting state in the morning.

Statistical analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS, Chicago, IL). The independent *t*-test was used to compare FMS patients and controls and to compare the serum CTX-1 level between patients with symptoms and patients without symptoms among FMS patients. For the comparison of features presented as categorical data, the χ^2-test was used. The Pearson correlation coefficient was used to assess the correlation between the serum CTX-1 level and the FMS-related features that are expressed as continuous or discrete data. Next, logistic regression analysis was used to examine the associations between FMS and potential risk factors. The results are presented as standardized coefficients and their 95% confidence intervals. A *P* value of less than 0.05 was considered significant for all parameters.

Results

Table 1 demonstrates the characteristics of the patients with FMS and the controls included in this study. Despite the fact that the patients with FMS and the controls were similar with regard to their age, social characteristics, and BMI, the serum CTX-1 level was significantly higher in the patients with FMS compared with the control group. The mean serum CTX-1 in patients with FMS was 340.2 ± 112.6 pg/ml compared with 283.6 ± 113.1 pg/ml in controls ($P = 0.004$). Also, the BDI in FMS patients was 19.1 ± 10.2 compared with 7.9 ± 4 in controls ($P < 0.001$). Regarding the sleep quality, the PSQI was also higher in patients with FMS than in controls (6.5 ± 3.5 vs. 1.9 ± 1.3, respectively). This difference was significant ($P < 0.001$). Among the FMS patients, 54% had a BDI score greater than 18 and 68% had a PSQI score greater than 5, but none of the individuals

Table 1 Descriptive statistics of the characteristics in FMS patients and controls

Items	FMS		Controls		*P*
	Range	Mean ± SD	Range	Mean ± SD	
Age (years)	26–48	37.9 ± 6.6	26–48	36.9 ± 6.8	0.391
BMI (kg/m^2)	24.1–31.2	29.4 ± 2	24.5–31.2	29.8 ± 1.7	0.246
Number of children	0–4	2.1 ± 1.5	0–4	1.9 ± 1.5	0.406
Education >high school [*n* (%)]		45 (45)		24 (48)	0.728
Employed [*n* (%)]		38 (38)		21 (42)	0.224
Married [*n* (%)]		70 (70)		32 (64)	0.458
Rural residence [*n* (%)]		49 (49)		29 (58)	0.298
Duration of FM (years)	5–15	10.3 ± 3.2			
BDI	2–36	19.1 ± 10.2	2–14	7.9 ± 4	<0.001
BDI>18 [*n* (%)]		54 (54)		0	<0.001
PSQI	1–12	6.5 ± 3.5	0–4	1.9 ± 1.3	<0.001
PSQI^{3}5 [*n* (%)]		68 (68)		0	<0.001
Serum CTX-1 (pg/ml)	145–513	340.2 ± 112.6	123–482	283.6 ± 113.1	0.004

BDI, beck depression inventory; FM, fibromyalgia; FMS, fibromyalgia syndrome; PSQI, pittsburg sleep quality index.

in the control group exceeded the cutoff point of either tests ($P < 0.001$).

As shown in Table 2, patients with FMS as compared with controls were more likely to have more postexertion pain ($P < 0.001$), confusion ($P = 0.015$), dizziness ($P = 0.033$), depression ($P < 0.001$), mood disturbance ($P < 0.001$), anxiety ($P < 0.001$), short memory difficulties ($P = 0.013$), long memory difficulties ($P = 0.023$), tension headache ($P = 0.016$), migraine headache ($P = 0.032$), Raynaud's phenomenon ($P = 0.033$), dysmenorrhea ($P = 0.037$), sleep disturbance ($P < 0.001$), restless leg syndrome (RLS) ($P = 0.007$), stiffness ($P = 0.015$), fatigue ($P < 0.001$), temperomandibular joint (TMJ) syndrome ($P = 0.013$), changes in appetite ($P = 0.018$), palpitation ($P = 0.038$), dyspepsia ($P = 0.030$), and irritable bowel syndrome (IBS) ($P = 0.011$). Patients with FMS had significantly higher FIQ, BDI, and HAQ scores than controls ($P < 0.001$).

Correlation analyses between serum CTX-1- and FMS-related features are shown in Table 3. The serum CTX-1 level was positively correlated with the VAS of pain ($r = 0.219$, $P = 0.028$), the VAS of fatigue ($r = 0.216$, $P = 0.031$), the VAS of global severity ($r = 0.240$, $P = 0.016$), the VAS of anxiety ($r = 0.248$, $P = 0.013$), the GSI score ($r = 0.243$, $P = 0.016$), the HAQ score ($r = 0.229$, $P = 0.022$), the FIQ ($r = 0.257$, $P = 0.010$), the BDI ($r = 0.270$, $P = 0.007$), the TP count ($r = 0.296$, $P = 0.003$), the TP score ($r = 0.286$, $P = 0.004$), and the PSQI ($r = 0.230$, $P = 0.021$).

Table 4 demonstrates the association between the serum CTX-1 level and FMS-related features. The mean serum CTX-1 level was also significantly higher in FMS patients with postexertion pain ($P = 0.010$), confusion ($P = 0.025$), dizziness ($P = 0.012$), depression ($P = 0.029$), mood disturbance ($P = 0.018$), anxiety ($P = 0.030$), short memory difficulties ($P = 0.017$), sleep disturbance ($P = 0.028$), RLS ($P = 0.016$), TMJ ($P = 0.043$), palpitation ($P = 0.022$), and IBS ($P = 0.028$) than in those without these symptoms. FMS patients who scored BDI greater than 18 also obtained a significantly higher mean serum CTX level than those who obtained a BDI score less than 18 ($P = 0.011$). Similarly, the mean serum CTX level was significantly higher in FMS patients with a PSQI score greater than 5 than in those with a PSQI score less than 5 ($P = 0.002$).

Table 2 Clinical features in fibromyalgia syndrome patients against controls

Items	FMS	Controls	*P*
Postexertion pain [*n* (%)]	61 (61)	7 (14)	<0.001
Confusion [*n* (%)]	30 (30)	6 (12)	0.015
Dizziness [*n* (%)]	22 (22)	4 (8)	0.033
Depression [*n* (%)]	54 (54)	0	<0.001
Mood disturbance [*n* (%)]	55 (55)	3 (6)	<0.001
Anxiety [*n* (%)]	53 (53)	5 (10)	<0.001
Short memory difficulties [*n* (%)]	33 (33)	7 (14)	0.013
Long memory difficulties [*n* (%)]	43 (43)	12 (24)	0.023
Tension headache [*n* (%)]	42 (42)	11 (22)	0.016
Migraine headache [*n* (%)]	44 (44)	13 (26)	0.032
Raynaud's phenomenon [*n* (%)]	22 (22)	4 (8)	0.033
Dysmenorrhea [*n* (%)]	32 (32)	8 (16)	0.037
Sleep disturbance [*n* (%)]	68 (68)	0	<0.001
RLS [*n* (%)]	27 (27)	4 (8)	0.007
Stiffness [*n* (%)]	53 (53)	16 (32)	0.015
Fatigue [*n* (%)]	84 (84)	11 (22)	<0.001
TMJ syndrome [*n* (%)]	19 (19)	2 (4)	0.013
Changes in appetite [*n* (%)]	24 (24)	4 (8)	0.018
Tremors [*n* (%)]	18 (18)	6 (12)	0.345
Palpitation [*n* (%)]	56 (56)	19 (38)	0.038
Dyspepsia [*n* (%)]	25 (25)	5 (10)	0.030
IBS [*n* (%)]	36 (36)	8 (16)	0.011
Genitourinary symptoms [*n* (%)]	7 (7)	2 (4)	0.466
FIQ (mean)	51.9 ± 11.3	7.4 ± 2.5	<0.001
GSI (mean)	5.3 ± 1.9	2.5 ± 1.7	<0.001
HAQ (mean)	1.8 ± 0.4	0.8 ± 0.3	<0.001

FIQ, fibromyalgia impact questionnaire; FMS, fibromyalgia syndrome; GSI, global self-rating index; HAQ, health assessment questionnaire; IBS, irritable bowel syndrome; RLS, restless leg syndrome; TMJ, temperomandibular joint.

Table 3 The correlation between serum CTX-1 with fibromyalgia syndrome-related features

Items	*R*	*P*
Age	0.071	0.480
Duration of disease	0.102	0.312
VAS of pain	0.219	0.028
VAS of fatigue	0.216	0.031
VAS of global severity	0.240	0.016
VAS of anxiety	0.248	0.013
GSI score	0.243	0.016
HAQ score	0.229	0.022
FIQ score	0.257	0.010
BDI	0.270	0.007
TPs count	0.296	0.003
TPs score	0.286	0.004
PSQI	0.230	0.021

BDI, beck depression inventory; FIQ, fibromyalgia impact questionnaire; FMS, fibromyalgia syndrome; GSI, global self-rating index; HAQ, health assessment questionnaire; PSQI, pittsburg sleep quality index; TPs, tender points; VAS, visual analogue scale.

Discussion

The degree of functional impairment observed in FMS is similar to that seen in patients with moderate to severe rheumatoid arthritis [18]. Thus, it has been postulated that patients with FMS may be at an increased risk of developing osteoporosis. Bone resorption and formation can be evaluated indirectly by the

Table 4 The association of serum CTX-1 with fibromyalgia syndrome-related features

Symptoms	Serum CTX-1 (mean ± SD)				*P*
	Symptom present		Symptom absent		
	N	Mean ± SD	*N*	Mean ± SD	
Postexertion pain	61	359.7 ± 104.7	39	309.6 ± 119	0.029
Confusion	30	376.6 ± 107.7	70	324.6 ± 111.8	0.033
Dizziness	22	386.5 ± 106	78	327.1 ± 111.6	0.028
Depression	54	366.6 ± 89	46	309.2129.4	0.010
Mood disturbance	55	363.9 ± 115.2	45	311.1 ± 103.2	0.019
Anxiety	53	365.9 ± 103.8	47	311.1 ± 113	0.014
Short memory difficulties	33	374.2 ± 117.8	67	323.4 ± 106.9	0.033
Long memory difficulty	43	365.9 ± 118.1	57	320.8 ± 105.2	0.047
Tension headache	42	371.4 ± 107.6	58	317.6 ± 111.6	0.018
Migraine headache	44	353.2 ± 113.7	56	329.9 ± 111.7	0.308
Raynaud's phenomenon	22	355 ± 117.4	78	336 ± 111.6	0.486
Dysmenorrhea	32	349.7 ± 118.9	68	335.7 ± 110.1	0.567
Sleep disturbance	68	360.8 ± 93.7	32	296.5 ± 136.4	0.007
RLS	27	378.9 ± 111.7	73	325.9 ± 110.2	0.036
Stiffness	53	351.1 ± 114.9	47	327.9 ± 109.9	0.304
Fatigue	84	353.2 ± 109.7	16	271.9 ± 105.6	0.007
TMJ affection	19	396.6 ± 106	81	327 ± 110.6	0.015
Changes in appetite	24	363.4 ± 114.5	76	332.9 ± 111.7	0.249
Fine tremors	18	342.3 ± 110.2	82	339.7 ± 113.8	0.931
Dyspepsia	25	369.4 ± 116	75	330.5 ± 110.5	0.135
Cardiovascular palpitation	56	361.4 ± 111.4	44	313.3 ± 109.5	0.033
IBS	36	371.2 ± 104.9	64	322.8 ± 113.8	0.038
Genitourinary symptoms	7	345 ± 133.2	93	339.8 ± 111.7	0.907
BDI > 18	57	363.2 ± 91.6	43	309.7 ± 130.4	0.018
PSQI $\geq$ 5 [*n* (%)]	68	360.8 ± 93.7	32	396.5 ± 136.4	0.007

BDI, beck depression inventory; FMS, fibromyalgia syndrome; IBS, irritable bowel syndrome; PSQI, pittsburg sleep quality index; RLS, restless leg syndrome; TMJ, temperomandibular joint.

measurement of serum and/or urinary concentrations of a number of parameters [19].

The bone is being remodelled continuously in a process by which osteoclasts resorb the bone tissue, and osteoblasts produce new bone matrix that is mineralized subsequently. Bone loss occurs when the balance shifts toward excess resorption [20].

Pyridinoline and deoxypyridinoline are cross-links of the mature form of collagen. The cross-links are released during collagen breakdown and thus can be used as potential markers of bone resorption. However, during bone resorption, these cross-links are released both in the free and the peptide-bound forms. These peptide-linked forms (C-telopeptide and N-telopeptide) have been shown to be more useful in the assessment of bone resorption [21,22].

Several markers have been described to measure bone metabolism. Type I collagen telopeptide fragments, C-telopeptide crosslaps of type I collagen (CTX-1), and C-terminal telopeptide of type I collagen (1CTP) are currently considered as the most sensitive markers of bone resorption and are released from bone type I collagen by different enzymatic pathways. CTX-1 is generated by cathepsin K, which is the key osteoclastic enzyme for systemic bone resorption [23].

In contrast, 1CTP is generated by matrix-metalloproteases, the activity of which plays an important role in the collagen degradation associated with rheumatoid arthritis (RA) [24].

Several studies have analyzed various bone turnover markers (BTMs) and their contribution to fracture risk, but the results of these studies have been inconsistent, not the least due to the use of different markers and different methodologies for their assessment. This has led to the recommendation for the standardization of BTM measurements in future studies with the use of serum CTX-1 as the standard bone resorption marker and serum procollagen type I N-terminal propropeptide (s-PINP) as the standard bone formation marker [25]. Most of the positive results with BTMs were for bone resorption markers, with an increased resorption marker predicting an increased fracture risk [26].

Contradictory data have been published regarding a possible association between fibromyalgia and osteoporosis. Most studies, however, have been performed on small-size samples.

To the best of our knowledge, our study is the first to assess CTX-1 levels in Egyptian patients with FMS.

The major finding of the current study was the significant increase in CTX-1 levels among FMS patients as compared with controls. These data might suggest an accelerated bone metabolism in these patients.

Also, we found that serum CTX-1 levels were positively correlated with the clinical symptom severity, the functional ability of patients, and the health-related quality of life.

In our study, further analysis of CTX-1 levels and correlations with the clinical characteristics of FMS revealed that the age of the patients and the duration of the disease were not correlated with CTX-1 levels. However, the CTX-1 level was positively correlated with pain, fatigue, the functional ability of the patients (HAQ, FIQ), GSI, and the TP count and score.

Mean serum CTX-1 levels were also significantly higher in FMS patients with postexertion pain, confusion, dizziness, mood disturbance, anxiety, short memory difficulties, TMJ, palpitation, and IBS than in patients without these symptoms.

Moreover, we found that FMS patients who were poor sleepers (higher PSQI score) had a significantly higher CTX-1 than patients without sleep problems.

Also, our results showed that FMS patients with RLS had a significantly higher CTX-1 than patients without RLS.

The current study evaluated the relation between the CTX-1 level and depression. The CTX-1 level was positively correlated with the Beck score of depression. Our results showed that CTX-1 was higher in depressed FMS patients than in nondepressed FMS patients.

Previous studies of bone turnover parameters have shown conflicting results in FMS. Appelboom and Schoutens [27]showed a higher Fogelman index and an increased 24-h pyrophosphate retention in the group of premenopausal FMS when compared with the control group using radioisotopic evaluation of skeletal remodeling, suggesting an accelerated bone metabolism in patients with FMS. The bone density (lumbar vertebrae and femoral neck) was not significantly different from that of control individuals.

El Maghraoui *et al.* [28]found that FMS patients had lower serum levels of CTX-1, and no significant statistical correlation was observed between the intensity of pain and fatigue and bone turnover parameters. They concluded that patients with FMS had low bone resorption and normal bone formation compared with the control group.

In a previous study, Jacobsen *et al.* [29] studied the bone mass and markers of bone metabolism in 12 premenopausal women with FMS and in healthy age-matched female control individuals. No differences were found in the lumbar BMD, the femoral neck BMD, serum levels of alkaline phosphatase, osteocalcin, and ionized calcium and phosphate.

Urinary excretion of both hydroxyproline and calcium relative to urinary creatinine excretion was significantly higher in patients with FMS. This probably reflected a lower physical activity in the patients with FMS. Jacobsen *et al.* [29] concluded that the bone mass and the turnover are generally not affected in premenopausal women with FMS.

Ribel-Madsen *et al.* [30] found low urinary concentrations of CTX-2 and CTX-1; significant inverse correlations were observed between CTX-1 and the intensity of fatigue. An inverse correlation between CTX-1 and the muscle strength was apparent, but it relied on extreme values from one patient, and no significant correlation was found between CTX-1 or CTX-2 and TPs or BMD in the FM group.

Sprott *et al.* [31] concluded that decreased levels of collagen cross-linking may contribute to the remodeling of the extracellular matrix and collagen deposition around the nerve fibers in FMS and contribute to the lower pain threshold at the TPs.

In another study, Mateos *et al.* [32] found that BMD and CTX-1 levels were similar in both groups. They considered that the association reported in other studies was merely circumstantial and not due to the intrinsic characteristics of these disorders.

Conclusion

We found a significant increase in the serum CTX-1 in FMS patients compared with controls, and this correlated with the disease severity. Increased CTX-1 may lead to the early development of osteoporosis. This study also confirmed the concept that FMS is a risk factor for osteoporosis.

Recommendation

More comprehensive and detailed studies are needed to determine the exact role of CTX-1 in FMS.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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