BRIEF PAPER

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Bone turnover and hormonal perturbations in patients with fibromyalgia

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ABSTRACT

Objective. *Studies of bone turnover in fibromyalgia (FM) have, to date, shown conflicting results. Although most patients with FM are women, only a few investigations have paid attention to the changes of sex hormones in FM. Moreover, FM is often viewed as a stress related disorder, and abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis have been found in FM. The aim of the study was to assess bone turnover using serum osteocalcin and CTx in patients with FM and study correlation between bone turnover parameters and parathormon and hormones of the HPA axis.*

Methods. *A total of 81 subjects participated in this study: 41 healthy volunteers and 40 patients with FM. Serum osteocalcin, crosslaps (C-telopeptide: CTx), parathyroid hormone (PTH), testosterone, estrogen, prolactin, FSH, and LH were measured. The mean age of the study population was 49.5 (7.6) years (32-69) and the mean disease duration was 8.1 (12.0) years (4.5-30.7).*

Results. *No difference between patients and controls were observed in serum calcium, phosphorus, creatinine, albumin, osteocalcin, testosterone, and urinary calcium. Patients had lower serum levels of CTx, estrogen, PTH and prolactin than controls and higher serum levels of LH and FSH with a significant statistical difference. No significant statistical correlation was observed between intensity of pain and fatigue and bone turnover parameters and PTH or hormones of the HPA axis.*

Conclusion. *Our study showed that patients with FM had low bone resorption and normal bone formation compared to a control group. This was not related to several hormonal perturbations observed in these patients and may reflect functional impairment as suggested in previous studies.*

Introduction

Fibromyalgia (FM) is a chronic musculoskeletal syndrome. The dominant features are widespread pain, with fatigue and evidence of pain amplification. It occurs more commonly in women and has a prevalence of 2% in the general population. Almost invariably symptoms persist at 5- and 10-yr follow-ups. The degree of functional impairment observed in FM is similar to that seen in patients with moderate to severe rheumatoid arthritis (1). Thus, it has been postulated that patients with FM may be at increased risk of developing osteoporosis. Bone resorption and formation can be evaluated indirectly by measurement of serum and/or urinary concentrations of a number of parameters (2). These markers are either enzymes involved in bone remodeling or bone matrix components released into the circulation during bone formation or resorption. Studies have demonstrated that osteocalcin (OC) is specific for bone, and that serum concentrations provide a measure of the bone formation. Pyridinoline and deoxypyridinoline are crosslinks of the mature form of collagen. The crosslinks 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 free and peptide-bound forms. These peptides linked forms (C-telopeptide and N-telopeptide) has been shown to be more useful in the assessment of bone resorption (2-6). Studies of bone mineral density (BMD) and bone turnover in FM have, to date, shown conflicting results (7-10).

Although most patients with FM are women, only a few investigations have paid attention to the changes of sex hormones in FM. Moreover, FM is often viewed as a stress related disorder, and abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis have been found in FM. The central stress axis, the HPA axis, seems to have an important role in FM. Some studies have suggested that patients with FM have decreased function of the HPA (11-16).

We therefore aimed to assess bone turnover using serum osteocalcin and CTx in patients with FM and study potential correlations between bone turnover parameters and parathormon and hormones of the HPA axis.

Patients and methods

A total of 81 subjects participated in this study: 41 healthy volunteers and 40 patients with FM.

Patients

Consecutive female patients with FM and attending our department in a three-month period were enrolled. All subjects fulfilled the American College of Rheumatology (ACR) criteria for FM (17). The diagnosis of FM was based on the typical features of the disease (chronic pain, fatigue, sleep and mood disturbance, irritable bowel syndrome). Major clinical conditions other than FM were excluded by physical examination and laboratory investigations of routine blood cells and differentials, red blood cells, packed cell volume and haemoglobin, baseline thyroid stimulating hormone, and antinuclear autoantibodies. Each patient had normal findings on radiography of the chest, hands, feet, and sacroiliac joints. Consent was obtained for all patients. Exclusion criteria were heavy smoking (> 10 cigarettes/day); alcohol intake; any drug treatment which can influence bone metabolism such as thyroid hormones, steroids, bisphosphonates, products containing vitamin D or its derivatives, calcium and magnesium; recent or past history of psychiatric disorders - for example, major depressive disorder, substance abuse, schizophrenic or paranoid disorder, personality disorder, and somatoform disorder; subjects with neurological, inflammatory, endocrine or clinically significant chronic disease, such as diabetes mellitus, rheumatoid arthritis, inflammatory bowel disease, and organic brain disorders; abnormal liver function tests, such as serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and c-glutamyltranspeptidase; and pregnant women. All subjects were Caucasians. Visual analog scale (VAS) questionnaires were used for self-measurement and subjects were instructed to rate the severity of each item at the exact moment of measurement. Pain was self-rated on a 100 mm horizontal VAS with end markers and terminal descriptors (left = no pain, right = most severe pain I have ever had). Fatigue was self-rated on a 100 mm VAS with end markers and terminal descriptors (left = no fatigue, right = most severe fatigue I have ever had).

Controls

The control group for BMD measurement corresponded to 41 female blood donors. The controls were age matched to the patients. The exclusion criteria were the same as the patients group. None of them had ever had chronic widespread pain nor fulfilled ACR criteria for FM and none was a regular drinker or had ever taken psychotropic drugs. None of them had history of inflammatory rheumatic disease or a condition responsible of bone loss.

Biological assessment

All samples were taken in the early morning. Premenopausal women were in the follicular phase of their menstrual cycle. Blood was collected in vacutainers without additive. After centrifugation at 1500xg for 10 min, serum was aliquoted and stored at -20°C. Serum concentrations of calcium, phosphorus, alkaline phosphatases, serum albumin, and erythrocyte sedimentation rate (ESR) were measured by standard methods. Serum osteocalcin, crosslaps (C-telopeptide: CTx), parathyroid hormone (PTH), testosterone, estrogen, prolactin, FSH, and LH were measured in 40 patients and 41 controls using electrochimiluminescence on ELECSYS 2010 analyser (Roche Diagnostics, Mannheim).

Statistical analysis

This cross-sectional study was conducted in different steps: the first step consisted of the description of the study population; in the second step, we compared biological data in patients and controls using the Student's t-test as all data had normal distribution; in the third step, we looked for correlations between bone turnover markers and age, disease duration, and biological data using the Pearson correlation coefficient. Results were considered to be significant when p values were less than 0.05. The Statistical Package for Social Sciences (SPSS, Chicago, IL) was used for data analysis.

Results

Forty female patients were recruited and compared to 41 controls. Results are expressed as mean (SD) [range]. The mean age of the study population was 49.5 (7.6) years (32-69) and the mean disease duration was 8.1 (12.0) years (4.5-30.7). Characteristics of the 40 patients and the 41 controls are shown in Table I. No difference between patients and controls were observed in serum calcium, phosphorus, creatinine, albumin, osteocalcin, testosterone, and urinary calcium. Patients had lower serum levels of CTx, estrogen, PTH and prolactin than controls and higher serum levels of LH and FSH with a significant statistical difference (Table II). No significant statistical correlation was observed between pain, fatigue or global health assessment and bone turnover parameters and PTH or hormones of the HPA axis.

Discussion

Our study showed decreased bone resorption and normal bone formation in a group of patients with FM compared to a control group. We found also that the patients with FM had lower levels of estrogen, prolactin and PTH and higher levels of FSH and LH than the control group.

Previous studies of BMD and bone turnover parameters have shown conflicting results in FM. Appleboom (18) showed using radioisotopic evaluation of skeletal remodeling higher Fogelman index and increased 24-hour pyrophosphate retention in the group of fibromyalgics (n = 28) when compared to a control group (n = 16) suggesting an accelerated bone metabolism in patients with FM. Bone density (lumbar vertebrae and femoral neck) was not significantly different from control subjects. Jacobsen (19) studied bone mass and markers of bone metabolism in 12 premenopausal women with FM and in healthy age matched female control subjects. No differences were found in lumbar bone mineral density, femoral neck bone mineral density, serum levels of alkaline phosphatase, osteocalcin, ionized calcium and phosphate. The urinary excretion of both hydroxyproline and calcium relative to urinary creatinine excretion was significantly higher in patients with FM. This was probably reflecting lower physical activity in the patients with FM. The

authors concluded that bone mass and turnover are generally not affected in premenopausal women with FM. Sprott *et al*. (20) took skin biopsy samples from the trapezius region of 8 patients with FM and collected urine from 55 control subjects and 39 patients with FM, and serum from 17 controls and 22 patients with FM. Pyridinoline (Pyd) and deoxypyridinoline (Dpyd), both of which represent products of lysyl oxidase-mediated crosslinking in collagen, were studied. Levels of hydroxyproline (Hyp), a collagen turnover marker, were also measured. The findings were related to creatinine levels, and the Pyd:Dpyd ratio was determined. They found highly ordered cuffs of collagen around the terminal nerve fibers by electron microscopic examination of biopsy tissue from all 8 patients with FM, but were not observed in any of the control skin samples. The Pyd:Dpyd ratios in the urine and serum and the Hyp levels in the urine were significantly lower in patients with FM than in healthy controls. They concluded that decreased levels of collagen crosslinking in FM may contribute to remodeling of the extracellular matrix and collagen deposition around the nerve fibers, and may contribute to the lower pain threshold at the tender points.

Our study failed to show any interrelation between pain, fatigue and bone turnover, PTH or hormones of the HPA axis. However, it showed several hormonal perturbations: lower serum levels of estrogen, PTH and prolactin than controls and higher serum levels of LH and FSH. There is no explanation for the higher frequency of FM in women, which suggests that sex hormones may have a role in the expression of the disease. Although the majority of FM patients are female, only a few investigations have paid attention to the changes of sex hormones in FM (21–23). Riedel and colleagues (24) investigated female FM patients and controls who were all in the follicular phase of their menstrual cycle. They found that FM patients had significantly lower estrogen levels despite elevated FSH levels. Korszun and colleagues (12) and Akkus and colleagues (11) found no differences from controls in values of FSH and LH in patients with FM. If the FSH and oestrogen values of female FM patients are compared during the follicular phase with the control group of women of the same age, significantly lower oestrogen plasma values are found with FM in spite of an elevated FSH level. Furthermore, the LH secretion is significantly reduced in female FM patients after the systemic administration of LHRH. An increased CRH activity caused by chronic pain might also explain this phenomenon.

In clinical practice, it is often observed that stress and chronic pain leads to a disturbance of gonadal function; in this connection, it has been experimentally demonstrated that CRH, and also prolactin on the hypothalamic level, reduces the gonadal function via the inhibition of LHRH secretion. Chronic stress is also often accompanied by lowered LH values. Recently, it could be shown that receptors for CRH are expressed in the ovary and CRH inhibits the FSH-stimulated oestrogen production (25).

In summary, our study showed that patients with FM had low bone resorption and normal bone formation compared to a control group. This was not related to several hormonal perturbations observed in these patients and may reflect functional impairment as suggested in previous studies even it was not correlated to the intensity of pain and fatigue in our study. However, longitudinal studies including higher number of patients are needed to defin-

Table I. Demographic and descriptive data of patients and controls.

	Patients n = 40	Controls n = 41
Age: years, m (SD)	49.5 (7.6)	49.2 (6.0)
Disease duration: years, m (SD)	8.1 (7.4)	-
BMI: Kg/ m^2, m (SD)	25.5 (4.4)	25.4 (4.1)
Menopause, n (%)	19 (50)	20 (50)
Age at menarche, m (SD)	12.91 (0.28)	13.14 (0.21)
Age of menopause, m (SD)	45.4 (8.1)	45.3 (8.7)
Intensity of pain (VAS): mm, m (SD)	76.8 (21.5)	-
Morning stiffness, n (%)	31 (77.5)	0 (0)
Fatigue, n (%)	30 (75)	0 (0)
Intensity of fatigue (VAS): mm, m (SD)	80.6 (26.3)	-
Skinfold tenderness, n (%)	34 (85)	0 (0)
Sleep disturbance, n (%)	33 (82.5)	0 (0)
Cigarette smoking, n (%)	0 (0)	0 (0)
Elementary school, n (%)	26 (46)	20 (44)
Secondary school, n (%)	10 (22)	13 (28)
University/High school, n (%)	4 (10)	13 (32)
Employed, n (%)	7 (17.5)	7 (17)
Retired, n (%)	3 (4)	2 (4)
Homemaker, n (%)	30 (75)	24 (58.5)

BMI: body mass index, VAS : visual analog scale.

Table II. Biological findings in patients and controls.

	Patients (n = 40)	Controls (n = 41)	p
Osteocalcin (ng/ml)	24.3 (4.1)	21.8 (5.3)	NS
CTx (ng/ml)	0.319 (0.1)	0.420 (0.1)	0.02
PTH (pg/ml)	47.6 (15.2)	56.7 (11.5)	0.04
Prolactin (IU/ml)	251.7 (156.3)	392.7 (85.2)	0.002
Testosterone (ng/ml)	3.9 (2,1)	3.4 (1.8)	NS
Estrogen (pg/ml)	28.1 (13.8)	35.7 (17.0)	0.001
FSH (IU/ml)	51.6 (3.6)	14.4 (2.6)	0.002
LH (IU/l)	21.7 (2.4)	9.3 (1.5)	0.002

Results are expressed as means (SD).

itively clarify the interrelations between bone turnover and the hormonal perturbations usually observed in patients with FM.

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