

Bone health in patients with fibromyalgia

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Objectives. To determine whether women with fibromyalgia are at increased risk of developing osteoporosis or osteomalacia.

Methods. Forty premenopausal women with fibromyalgia and 37 age-matched female controls were studied. Broadband ultrasound attenuation (BUA) and velocity of sound (VOS) were measured at the calcaneum and bone mineral density was measured at the forearm and lumbar spine using dual-energy X-ray absorptiometry. Serum calcium, alkaline phosphatase, γ -glutamyl transferase, 25-hydroxyvitamin D and plasma viscosity were measured in all subjects and parathyroid hormone was measured in subjects recruited in the latter part of the study.

Results. Seventeen patients with fibromyalgia syndrome and seven controls had 25-hydroxyvitamin D concentrations < 20 nmol/l ($P < 0.015$) and in three FMS patients serum parathyroid hormone was raised. Bone density in fibromyalgia patients was slightly lower at the mid-distal forearm but comparable to that in controls at other sites.

Conclusions. There is no reason to recommend routine bone densitometry in fibromyalgia patients. However, vitamin D subnutrition is common in these patients and this should be sought.

KEY WORDS: Fibromyalgia, Bone density, Vitamin D, Osteoporosis.

Fibromyalgia syndrome (FMS) is a chronic musculo-skeletal syndrome. The dominant features are widespread pain, with fatigue and functional impairment with evidence of pain amplification. It occurs more commonly in women and has a prevalence of 2% in the general population [1]. Almost invariably symptoms persist at 5- and 10-yr follow ups [2, 3]. The degree of functional impairment is similar to that seen in patients with moderate to severe rheumatoid arthritis.

As patients with FMS have impaired mobility, we postulated that they may be at increased risk of developing osteoporosis. Studies of bone mineral density (BMD) in FMS have, to date, shown conflicting results [4, 5]. We therefore aimed to assess bone density using various techniques in patients with FMS and also to look for secondary causes of osteopenia. In addition, as these patients might be less mobile and therefore get less sunlight exposure, we also looked for evidence of osteomalacia.

Methods

Patients

Fibromyalgia patients were identified from a computerized diagnostic index in the Rheumatology Unit at Ninewells Hospital. They had been diagnosed in accordance with the American College of Rheumatology (ACR) criteria for the diagnosis of FMS [6]. Initially we targeted premenopausal female patients aged between 40 and 50 yr and later dropped the lower age to 35 yr in order to have the required number to show a difference according to the power calculation (see Statistics, below). We included only patients who were premenopausal, as assessed by a history of regular menses; if in doubt, and for women who had had a hysterectomy, levels of luteinizing hormone and follicle-stimulating hormone were assessed. They were excluded if found to be postmenopausal. We excluded postmenopausal females in this study because bone loss in the first decade after the menopause is rapid and we felt that it would be difficult to recruit well-matched controls. We had also anticipated that many potential postmenopausal patients would be excluded because of the

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use of hormone replacement therapy. Our study was designed for premenopausal women because BMD should change little at this age (35–50 yr) and control subjects relevant to the fibromyalgia patients would be recruited more readily.

General practitioners were sent details of the study with respect to each patient. Unless the general practitioner contacted us within 2 weeks to say that the study was not suitable for the patient, each patient was contacted by post with details of the study and invited to participate, provided that she was premenopausal, was not pregnant and did not have other conditions known to affect bone metabolism.

Eighty-five suitable patients were identified. Three general practitioners replied to say that their patients were not suitable for the study. Eighty-two FMS patients were contacted. Ten failed to respond even after a reminder letter, giving a response rate of 88%. Five patients responded indicating no interest in the study. Twenty-six FMS patients were excluded from the study; 15 were on hormone replacement therapy, eight were postmenopausal, one was found to have rheumatoid arthritis, one was taking tamoxifen for breast cancer and one was on bisphosphonate treatment. There were no patients on regular corticosteroid therapy, with hyperthyroidism, inflammatory bowel disease, primary biliary cirrhosis or known alcohol abuse.

Controls

Forty-two age-matched premenopausal female controls were recruited. Ten were recruited from friends and relatives of the patients, and 32 from friends and colleagues of controls and also from hospital and medical school employees. One control subject was later found to have had two raised plasma viscosity results (≥ 1.72 mPa/s) and was excluded from the data analysis. Four controls were excluded from the analysis because they had six or more tender fibromyalgia sites.

No controls needed to be excluded because of a Stanford Health Assessment Questionnaire (HAQ) score of 0.25 or more. Thirteen control subjects had a Fibromyalgia Impact Questionnaire (FIQ) score greater than 1. Scores for these subjects ranged from 1.04 to 4.0 out of a possible 10. Most of the score derived from questions on general aspects, such as tiredness or anxiety. All the control subjects were working and we felt that working women could well be tired, tense and perhaps a little depressed. There was little contribution to the score from questions on pain or stiffness or the ability to carry out everyday tasks. These control subjects were not excluded from the data analysis.

Study visit

The same researcher (PAM) saw all subjects, performed all the bone density measurements and the fibromyalgia tender spot counts. Only one study visit was required for each subject. During the visit, informed consent was obtained, the study was explained and any questions were answered. A structured history was taken with details of weight, height, age at menarche, alcohol and smoking habits, medications including any past use of steroids, calcium intake, family history of osteoporosis, other medical problems and, for FMS patients, the time since fibromyalgia was diagnosed. Alcohol status was assessed in three categories: regular alcohol consumption (1–14 units per week), occasional drinks only, and never drinks alcohol. The smoking status was assessed in three categories: current smokers, past smokers, and never smoked.

Functional ability and mobility assessment

The functional ability and mobility of each subject was assessed by four methods in order to get results that were as accurate as possible. Participants were classified into one of four functional classes: 1 was normal, 2 represented normal function despite handicap, 3 reflected the ability to carry out few or none of the duties of the usual occupation or self-care, and 4 was total or almost total incapacity, bedridden or confined to a wheelchair. We also used the modified Stanford HAQ [7], the McAlpine mobility score [8] and the FIQ [9]. Although HAQ is validated only for patients with rheumatoid arthritis, we felt it offered useful additional information on the activities of daily living of the subjects. Using 10-point visual analogue scales, the FMS patients assessed their pain and the perceived activity of their fibromyalgia over the preceding 7 days. The number of fibromyalgia tender points was assessed in each participant, as indicated in the ACR criteria for the diagnosis of FMS, with the total possible score of 18 tender points [6].

Laboratory investigations

All participants had blood taken for measurement of plasma viscosity and serum calcium, alkaline phosphatase, γ -glutamyl-transferase (GGT) and 25-hydroxyvitamin D (25-OH vitamin D). Midway through the study we found that there was a significant number of patients with low levels of serum 25-OH vitamin D. All the subsequent subjects included in the study had the serum parathyroid hormone level assessed routinely.

Bone densitometry

CUBAClinical ultrasound. All the quantitative ultrasound measurements of the calcaneus were carried out with the McCue CUBAClinical dry system according to the manufacturer's instructions (McCue Plc, Winchester, UK). Broadband, single-element, flat (unfocused) immersion-type transducers are used in this system. Centre frequency was 1.0 MHz and acoustic intensity was 0.28 W/cm². Broadband ultrasound attenuation (BUA) was reported in dB/MHz and velocity of sound (VOS) was reported in m/s. The measurement error coefficient of variation of the BUA was found to be 3.5% and that of VOS 0.5%. Quality assurance and quality control checks were carried out each day. The non-dominant heel was measured unless it was the site of a previous fracture or was unsuitable.

Dual-energy X-ray absorptiometry: Lunar DPX Alpha. For the measurements of BMD and bone mineral content (BMC) of the posterior–anterior lumbar spine, we used the Lunar DPX Alpha (Lunar Corp., Madison, WI, USA) with software version 1.15. Photon energies were 38 and 70 keV and voltage 76 kVp. The machine was calibrated before scanning each day and the Lunar spine aluminium phantom was scanned to monitor any drift. The measurement error coefficient of variation (based on 10 subjects, each having two lumbar spine scans with repositioning between scans) for L2–L4 was 1.54% for BMC and 1.38% for BMD. Patient results are expressed as BMC (g) and as BMD (g/cm²).

Subjects were scanned in indoor clothing with no metal objects at the scan site and the recommended Lunar scanning procedure was used. Medium scan mode was used for all subjects and current was 750 or 3000 μ A depending on the body mass index (BMI) of the subject.

Dual-energy X-ray absorptiometry: Osteoscan pDXA. For the peripheral scanning at the radius we used the Osteoscan pDXA (NIM S.r.l., Verona, Italy, supplied by Vertec

Scientific, Reading, UK) [10] with software version 2.1x. Photon energies were 27 and 52 keV. The machine was calibrated prior to scanning and the supplied phantom was scanned. Average measurement error coefficient of variation was 2.6% for ultradistal BMC and 1.8% for ultradistal BMD, and 2.1% for mid-distal BMD and 1.9% for mid-distal BMD. The non-dominant wrist was measured unless there had been a fracture, and the manufacturer's recommended procedure was followed. Results were expressed as BMC (mg) and as standardised BMD (mg/cm²).

Statistics

We calculated the number needed to be studied on the basis that it should permit the detection of a difference in bone density at the lumbar spine of one standard deviation or more between the FMS patients and the control group. A *P* value of 0.05 or less was taken as statistically significant with a power of 90%. On this basis, a minimum of 23 subjects would be needed in each group. We preferred to recruit as many patients as practical as only a limited number of fibromyalgia patients fulfilled our inclusion criteria, with the object of detecting an even smaller difference. We stored and analysed all the data using SPSS version 10 (SPSS, Chicago, IL, USA). Normality was tested using the Kolmogorov–Smirnov test. Normally distributed data were analysed using the *t*-test for two independent samples, while the non-normally distributed data were analysed using the Mann–Whitney test. Bone density was compared using analysis of covariance with BMI and age as covariates. We used the χ^2 test to assess frequency differences between the groups.

Ethics

The study protocol was approved by the Tayside Committee on Medical Research Ethics.

Results

Table 1 shows the demographic, clinical and laboratory variables in the two groups. No significant differences were found in age at menarche or history of hysterectomy. Although FMS patients had reported more family history of osteoporosis than controls (25 and 10.8% respectively), the difference did not reach a significant level (*P* = 0.09).

Patients with FMS were more likely to be smokers compared with controls (52.5 and 18.9% respectively, *P* = 0.006). Patients were found to have a higher BMI compared with controls (28.9 and 25.8 respectively, *P* = 0.016). FMS patients were found to be more likely to have had previous steroid therapy compared with controls (42.5 and 8.1% respectively, *P* = 0.001). However, FMS patients were significantly less likely to take alcohol on a regular basis (27.5 and 78.4% respectively, *P* < 0.001).

As expected, patients with FMS had significant mobility and functional impairment as assessed by the McAlpine scale, functional class, HAQ score and FIQ score (*P* for all < 0.001). FMS patients also had significantly more tender FMS points and sleep disturbance (*P* < 0.001).

Seventeen FMS patients and seven controls had 25-OH vitamin D concentrations < 20 nmol/l ($\chi^2 = 5.93$, *P* < 0.015). Although all the other laboratory findings were within normal limits, we found that patients with FMS had significantly higher plasma viscosity, serum GGT and serum alkaline phosphatase than controls (*P* = 0.001, 0.017 and 0.02 respectively). Three of 23

TABLE 1. Demographic, clinical and laboratory results in FMS patients and controls

	FMS group	Control group	<i>P</i>
Number	40	37	
Age (yr)	42.5 (3.6)	42.5 (4.3)	0.94
BMI (kg/m ²)	28.9 (6.0)	25.8 (5.4)	0.016
Current smokers	21 (52.5%)	7 (18.9%)	0.006
Regular alcohol intake (1–14 units/week)	11 (27.5%)	29 (78.4%)	< 0.001
Age at menarche (yr)	12.7 (1.4)	13.0 (2.8)	0.28
Hysterectomy	6 (15%)	2 (5.5%)	0.27
Previous fracture	14 (35%)	5 (16.2%)	0.03
Family history of osteoporosis	10 (25%)	4 (10.8%)	0.09
Previous steroid intake	17 (42.5%)	3 (8.1%)	0.001
McAlpine scale (number impaired)	33 (82.5%)	0%	< 0.001
Functional class (number impaired)	32 (80%)	0%	< 0.001
Number of tender FMS points (out of 18)	13.6 (3.3)	0.76 (1.2)	< 0.001
Sleep problem (out of 10 on VAS)	6.68 (2.1)	1.89 (2.2)	< 0.001
Current HAQ (score out of 3)	1.58 (0.77)	0.01 (0.03)	< 0.001
Current FIQ (score out of 10)	6.47 (2.19)	0.72 (0.87)	< 0.001
Mean disease duration (yr)	3.98 (2.6)	NA	NA
Pain score (out of 10 on VAS)	6.88 (2.4)	NA	NA
Patient global assessment (out of 10 on VAS)	6.3 (2.5)	NA	NA
Plasma viscosity (mPa/s)	1.65 (0.08)	1.59 (0.06)	0.001
Serum GGT (U/l)	30.8 (34)	17.9 (11)	0.017
Serum alkaline phosphatase (U/l)	71.9 (24.4)	61.3 (13.6)	0.02
Corrected serum calcium (mmol/l)	2.36 (0.09)	2.35 (0.07)	0.34
Serum 25-OH vitamin D < 20 nmol/l	18 (45%)	7 (18.9%)	< 0.015
Serum parathyroid hormone (pmol/l) ^a	3.7 (2.5)	4.0 (1.8)	0.25

Data are number (percentage) or mean (s.d.).

^a23 FMS patients and 31 control subjects.

TABLE 2. Bone assessment measurements for FMS patients and control subjects: mean (s.d.) analysis of covariance with age and BMI as covariates

	FMS group	Control group	<i>P</i>
Number	40	37	
Ultrasound BUA (dB/MHz)	90.26 (16.7)	92.61 (16.6)	0.056
Ultrasound VOS (m/s)	1652 (28)	1665 (31)	0.059
Ultradistal sBMD (mg/cm ²)	395.4 (56)	389.8 (40.6)	0.535
Mid-distal sBMD (mg/cm ²)	699 (45)	724 (43)	0.023
L2–L4 spine BMD (g/cm ²)	1.248 (0.14)	1.24 (0.12)	0.489

FMS patients (16.7% of those with low serum 25-OH vitamin D, 7.5% of all the FMS patients) and one of 31 control subjects were regarded as having biochemical osteomalacia, as defined by raised serum parathyroid hormone in the absence of hypercalcaemia.

Apart from the BMD in the mid-distal radius, which was significantly lower in the FMS patients compared with controls ($P=0.023$), no significant difference was found in measures of BMD (Table 2). Three patients with FMS and two controls had a T score below -1.5 at least one site; one of these controls had a T score below -2.5 at the mid-distal radius.

There were no significant differences in the parameters studied between FMS patients with low serum 25-OH vitamin D (<20 nmol/l) and those with higher levels (≥ 20 nmol/l) (Table 3). Although the

mean serum parathyroid hormone level was found to be higher in the patients with low 25-OH vitamin D (4.27 ± 3 and 2.86 ± 0.99 pmol/l respectively), the difference did not reach statistical significance ($P=0.48$).

Discussion

This study has demonstrated several interesting findings. The first of these is the significantly greater proportion of FMS patients with low 25-OH vitamin D levels. There is seasonal variation in 25-OH vitamin D levels; the median month of first visit for the FMS patients was March 2001 and for the control subjects it was May 2001. However, although one might expect this to affect mean 25-OH vitamin D concentrations, values below the expected range are of clinical significance irrespective of time of year [11]. There were no significant differences in parathyroid hormone or corrected calcium. However, three of the patients did have biochemical osteomalacia compared with one control patient. Low 25-OH vitamin D concentrations are likely to be due to less sunlight exposure in the less physically active FMS patients, though we did not look for alternative explanations, such as malabsorption. This finding of lower 25-OH vitamin D concentrations in FMS patients, if confirmed, may be important in the investigation and management of FMS in future. The

TABLE 3. Comparison of patients with FMS who had plasma 25-OH vitamin D <20 and ≥ 20 nmol/l

	25-OH vitamin D <20 nmol/l	25-OH vitamin D ≥ 20 nmol/l	<i>P</i>
Number	18 (45%)	22 (55%)	
Mean 25-OH vitamin D (nmol/l)	14.96 (3.4)	36.46 (13.1)	
Mean (s.d.) age (yr)	43.6 (2.9)	41.6 (3.9)	0.08
Mean disease duration (yr)	3.64 (2.6)	4.25 (2.5)	0.45
Mean BMI (kg/m ²)	29.1 (5.9)	28.9 (6.2)	0.94
Current smokers	11 (61.1%)	10 (45.5%)	0.18
Regular alcohol intake	6 (33.3%)	5 (22.7%)	0.33
Mean age at menarche (yr)	12.4 (1.4)	12.9 (1.4)	0.27
Hysterectomy	4 (22.2%)	2 (9.1%)	0.25
Previous fracture	2 (11.1%)	1 (4.5%)	0.72
Family history of osteoporosis	5 (27.8%)	5 (22.7%)	0.23
Previous steroid intake	7 (38.9%)	10 (45.5%)	0.68
McAlpine scale (number impaired)	15 (83.3%)	18 (81.8%)	0.39
Functional class (number impaired)	14 (77.8%)	18 (81.8%)	0.43
Number of tender FMS points (out of 18)	13.4 (3.7)	13.7 (2.9)	0.95
Sleep problem (out of 10 on VAS)	6.1 (2.3)	7.1 (1.9)	0.13
Current HAQ score (out of 3)	1.56 (0.88)	1.59 (0.69)	0.99
Current FIQ score (out of 10)	6.22 (2.6)	6.68 (1.8)	0.83
Pain score (out of 10 on VAS)	6.78 (2.9)	6.95 (2.1)	0.87
Patient global assessment (out of 10 on VAS)	6.17 (2.6)	6.41 (2.5)	0.71
Plasma viscosity (mPa/s)	1.65 (0.09)	1.64 (0.08)	0.87
Serum alkaline phosphatase (U/l)	71.8 (18.2)	71.9 (28.9)	0.99
Corrected serum calcium (mmol/l)	2.38 (0.08)	2.35 (0.09)	0.27
Serum parathyroid hormone (pmol/l)	4.27 (3.0)	2.86 (0.99)	0.48
Ultrasound BUA (dB/MHz)	91.61 (16.3)	89.2 (17.3)	0.82
Ultrasound VOS (m/s)	1660 (22)	1645 (31)	0.08
Ultradistal sBMD (mg/cm ²)	400.8 (67)	391.0 (46)	0.86
Mid-distal sBMD (mg/cm ²)	697 (42)	701 (49)	0.76
L2–L4 spine BMD (g/cm ²)	1.267 (0.15)	1.232 (0.14)	0.44

Data are number (%) or mean (s.d.).

difference in alkaline phosphatase was matched by a difference in GGT, suggesting a hepatic rather than a bony origin. The difference in GGT is clearly not explained by alcohol consumption and there did not appear to be any difference in the use of enzyme-inducing drugs, but it may be explained by the difference in smoking habits.

Bone densitometry showed a difference in density only at the mid-distal site in the radius. This site mainly reflects cortical bone and indicates long-term rather than short-term bone loss. Ideally, we would also have measured BMD at the hip. A pilot study [4] suggested lower spine BMD in FMS, and this was the primary reason for concentrating on the spine. Although the precision of BMD measurement is greater at the spine, measurements at the hip may have provided further useful information.

No significant differences in disease or lifestyle parameters were apparent between fibromyalgia patients who had high and those who had low serum 25-OH vitamin D levels. However, as a group, the FMS patients were much more likely to be smokers, to have had a previous fracture, to have used steroids, to have a family history of osteoporosis and to be less physically active than controls (paradoxically, alcohol intake was lower in FMS patients). Some of these may represent separate risk factors for osteoporosis; most are possibly a direct consequence of fibromyalgia or, in the case of fractures, perhaps a cause [12].

It would appear, therefore, that although this study failed to demonstrate conclusive evidence of reduced bone density in premenopausal women with fibromyalgia, there are definite indicators, in terms of both lifestyle and low serum 25-OH vitamin D, that these patients had a likelihood of poorer bone health in the future. A follow-up study in postmenopausal patients is indicated to test this hypothesis. These patients were specifically excluded from our current study.

An interesting but unexpected finding was the significantly higher plasma viscosity (although still within the normal range) in FMS patients. This may represent low-grade inflammation as part of their clinical condition, or may reflect a higher degree of cardiovascular risk, perhaps related to their smoking. Recent work has suggested that patients with widespread pain syndromes have a higher overall mortality rate. Serum alkaline phosphatase and GGT levels were also raised, and again may represent low-grade inflammation or may be related to smoking. Again, further work in these areas would be justified.

Symptoms in patients with low serum 25-OH vitamin D did not differ significantly from those in patients with higher levels. Following the study, 18 FMS patients and two controls with serum 25-OH vitamin D concentrations less than 19 nmol/l were given a single injection of calciferol 300 000 units. Eight patients and no controls felt subjective improvement, and in three improvement persisted at 3 months. Those who had initial symptomatic benefit had a mean (S.D.) serum parathyroid hormone concentration of

5.3 (3.04) pmol/l compared with 3.46 (2.4) pmol/l in those who showed no response. Three months after the injection there was no change in HAQ or FIQ scores following calciferol, and serum alkaline phosphatase paradoxically rose, although this rise was confined to those who claimed no symptomatic relief.

It is conceivable that patients with FMS who have an 'abnormality' identified and are given an injection for this may well have a marked placebo response; further controlled studies are again indicated, although there might be an ethical problem in denying treatment in patients with low serum 25-OH vitamin D in a control group. In the meantime, we draw attention to the frequency with which we found vitamin D subnutrition in fibromyalgia patients.

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