Summary
Fibromyalgia (FM) is a syndrome characterised by the presence of diffuse chronic body pain which is associated with tenderness at certain sensitive points. Symptoms such as fatigue, altered sleep patterns or depression reduce the quality of life of these patients, reducing their physical activity. This may enhance the risk of osteoporosis. Various works have analysed the bone mass and levels of vitamin D in patients with FM, but the results are not conclusive.

Key words: fibromyalgia, osteoporosis, vitamin D.
The sum of these factors leads to the suspicion that patients with FM may have an increased risk of having OP. Various studies have been carried out which analyse bone mineral density (BMD) in patients with FM, but the results obtained have been uncertain. This is why we wished to carry out a review of the literature on this matter.

**Levels of vitamin D in patients with fibromyalgia**

Patients with FM are physically inactive, which results in a lower exposure to sun, and, therefore, a higher risk of hypovitaminosis D. A deficiency in vitamin D in these patients may increase musculoskeletal alterations, and the risk of falls.

Some works have shown a relationship between FM and low levels of vitamin D. Al-Allaf et al. determined the levels of 25 hydroxyvitamin D (25-OH)D in 77 premenopausal women, of whom 40 had FM, with the other 37 being healthy. They found a high prevalence of hypovitaminosis D (defined as 25-OH < 8 ng/ml) in the FM group (45%) compared with the control group (19%) (p< 0.015). Huisman et al. analysed the levels of vitamin D metabolites (25-OH and 1,25 OHD) in 25 women with FM and a similar number of women with Systemic lupus erythematosus (SLE), finding no differences; the prevalence of hypovitaminosis D (defined in this case as 25-OH < 20 ng/ml) was high in both groups (48% FM, 58% SEL). According to the authors the use of drugs such as hydrochloroquine, which modifies the conversion of 25-OHD to 1,25-OHD, may explain the deficiency in SEL, but in FM it may be due to other factors such as lower exposure to sun or to dietary disorders.

A more recent work, carried out in 75 caucasian patients with FM (5 men and 70 women), found a high prevalence of hypovitaminosis D in this population. Specifically, 13% of the cases had 25-OH < 10 ng/ml, 56% between 10-20 ng/ml and only 31% with levels of ≥ 20 ng/ml. Despite having made an assessment using the FIQ scale to measure the impact of FM on the quality of life (state of health and functional affection in patients with FM), no relationship was found between the levels of vitamin D and the musculoskeletal symptoms.

We would now like to mention the works of other authors who have analysed the levels of vitamin D in patients with chronic pain, although not necessarily with FM. Plotnikoff et al. determined the prevalence of hypovitaminosis D in 150 patients of both sexes and of 6 ethnic groups, who suffered non-specific persistent (> 2 months) musculoskeletal pain and which did not respond well to standard treatment. 93% of the total of these patients had low levels of vitamin D (25-OH < 20 ng/ml), specifically, 83% of the white patients, 89% of the Asians, and 100% of the African-Americans, Native Americans and Hispanic patients. There were no differences by sex. Block et al., cognisant of this study, determined the levels of vitamin D in 101 white patients of both sexes who suffered generalised non-specific chronic musculoskeletal pain. Two thirds of these patients (66) met the ARC criteria for FM and the remaining third formed the control group. The average level of vitamin D was similar in both groups, although the prevalence of hypovitaminosis D (25-OH < 20 ng/ml) was higher in the FM group than in the control group (48% vs 28%). Levels lower than 10 ng/ml were detected in 12% of the patients with FM, as against 3% in the control group. In 2008, Mouyis et al. compared the levels of 25-OHD in patients diagnosed with OP/osteopenia (n= 122) with a group of rheumatology patients followed up in an outpatients clinic (n= 141), observing that the levels of 25-OHD were significantly lower in the rheumatology patients. Specifically, those subgroups with inflammatory arthritis and chronic pain/FM had lower levels. More recently, McBeth et al. analysed levels in 3,075 people (8.6% with chronic diffuse pain, 50.4% with “other pain” which did not satisfy the criteria for diffuse chronic pain, and 41% controls) observing that, after adjusting for age and physical activity those patients with “other pain” and with chronic diffuse pain had lower levels of 25-OHD than the control group. A study carried out in the British population by Atherton et al. in 2009, in people of both sexes, found an inverse relationship between levels of vitamin D (25-OHD) and the suffering of chronic diffuse pain, but only in women. However, this relationship disappeared after adjusting for confusion factors. Tandeter et al. analysed the possible relationship between low levels of vitamin D and non-specific musculoskeletal pain (including patients with FM) in premenopausal women. They analysed this relationship in 68 women with FM and 82 without, not finding a relationship in either. Neither did Warner et al., comparing 184 patients with diffuse pain and 104 with osteoarthritis (taken as the control group) find a difference in 25-OHD between the two groups (29.2 ng/ml vs 28.8 ng/ml; p= 0.78). Nor were there differences in the percentages of patients with levels of 25-OHD ≤ 20 ng/ml (29% in patients with diffuse pain and 20% in those with osteoarthritis; p= 0.09). These authors administered vitamin D supplements, as opposed to a placebo, in 50 of their patients with diffuse pain and levels of 25-OHD ≤ 20 mL, over 3 months, confirming that the treatment with vitamin D did not have any effect on the pain in comparison with the placebo. In accord with these works, Ulusoy et al. compared, in 2010, the levels of 25-OHD in 30 women with FM compared with 30 healthy women of the same age, without finding any differences. Neither did Rzende et al. find any such differences in a transverse study which compared levels of 25-OHD in 87 patients with FM with a control group made up of participants without chronic musculoskeletal pain. The majority of these works failed to conclude that the prevalence of hypovitaminosis D was higher in patients with FM, although the studies are quite heterogeneous.
Fibromyalgia and osteoporosis

FM and OP share risk factors in common, and some medicines which alleviate the symptoms of FM may alter bone metabolism. Thus it has been suggested that the incidence of OP may be increased in those patients with FM.

1. Sex

Both OP and of FM are predominant in women. A study carried out by Yunus to evaluate the role of sex in FM indicated a 9:1 proportion in favour of women. It is also calculated that OP is 3 times more frequent in women than in men.

2. Age

Both the prevalence of OP, and that of FM, increase with age. In the study of Wolfe FM reached its maximum prevalence between the ages of 60 and 79 years. A later study by White confirmed that the symptoms of FM intensify with age. Age is also a clear risk factor for the development of osteoporosis.

3. Hygiene-dietary habits and lifestyle factors

Smoking exacerbates the pain symptoms in patients with FM and its deleterious effects on bone are well known.

It has been demonstrated repeatedly that physical exercise has a beneficial role in the attainment of peak bone mass, and that it is associated with an increase in bone mineral density (BMD). Physical inactivity is common in women with FM, often the consequence of pain, which constitutes another risk factor for the development of osteoporosis.

Dietary disorders may influence the development of osteoporosis. In FM, a higher prevalence of irritable bowel syndrome has been described, which is frequently associated with lactose intolerance, which can cause BMD loss in these patients.

Patients with FM have a higher risk of anxiety-depressive disorders. The association between depression and changes in bone mass has been well documented. Depression may take place in a weakened state, with protein deficiency, a decrease in calcium and vitamin supply and a reduction in levels of IGF-1. In addition, depression is associated with other risk factors for osteoporosis, such as physical inactivity due to fatigue, pain, quality of sleep and symptoms of depression.

4. Hormonal factors

In FM, there are neuroendocrine alterations which may favour the development of osteoporosis.

A) Sex hormones:

A study has evaluated the reproductive history of women between 35 and 74 years of age with FM (n= 36), with chronic diffuse pain without FM (n= 44), and without chronic pain (n= 408), finding that the women with FM had a later menarche (OR= 2.2 for > 14 years). Another work has determined the levels of adrenal androgens and its metabolites in 57 women with FM and 114 healthy controls. The levels of dehydroepiandrosterone (DHEA) were lower in the premenopausal (2.4 vs 4.8 μmol/l; p< 0.0001) and postmenopausal patients (1.2 vs 2.4 μmol/l; p< 0.001) with FM compared with their controls. Levels of testosterone were lower in premenopausal women with FM, but not in the postmenopausal women (2.36 vs 4.93 pmol/l; p< 0.0001). These results suggest adrenocortical hypofunction of the sex steroid metabolism, which could have an influence on the bone.

B) IGF-1:

The insulin-like growth factor type 1 (IGF-1) stimulates bone formation, exerting an anabolic influence on the bone. Its deficiency has been related to the development of OP. Some studies indicate that blood levels of IGF-1 are reduced in FM. This may constitute a risk factor for the development of low bone mass. Bennett et al. have shown that in 500 women with FM, as against 120 healthy women, levels of IGF-1 are lower in the patients (138 ± 56 ng/ml vs 215 ± 86 ng/ml; p< 0.001), whilst a more recent study describes levels of IGF-1 26% lower in women with FM compared with healthy women.

5. Use of medication

Certain drugs used in the treatment of FM may alter bone metabolism.

The anti-depressive selective serotonin reuptake inhibitors reduce the symptoms of FM. It has been reported that these drugs may reduce BMD. In addition, they increase the risk of amenorrhea. The benzodiazepines, well used in FM, are associated with a higher risk of falls and bone fractures. The anti-epileptics, used in the treatment of neuropathic pain, may cause hypovitaminosis D and osteomalacia.

Studies of bone mass in patients with fibromyalgia

The first authors who studied the alterations in bone metabolism in patients with FM were Appelboom et al., in 1990 analysing the BMD, using DXA in the lumbar spine (LS) and hip, of 44 premenopausal women of 26-50 years of age (28 with FM and 16 controls with other soft tissue rheumatisms). No differences were found in bone mass between the two groups in any location, after adjusting for the degree of physical activity and diseases or treatments which could modify bone metabolism. However, they did report an increase in bone remodelling in patients with FM, determined using radioisotopes (pyrophosphate bonded with technetium [Tc-PPi]) with a higher retention of Tc-PPi. In a later study, the BMD in LS measured by DXA was analysed in 24 women with FM and 48 healthy women (30-60 years of age). Stratifying the women by decades of age, they found that the women with FM had, at all ages, a lower bone mass in the LS (T-score = -0.31 vs -0.16 between 31- and 40 years,
-0.19 vs 0.04 between 41 and 50 years and -1.40 vs -0.25 between 51 and 60 years). In the femoral neck (FN) however, they only found differences in the decade 51-60 years (T-score = -1.97 vs -0.9; p< 0.005).

Another work\(^6\) studied, using ultrasound (US) of the calcaneum, 116 women with FM and 141 control women, all of whom were premenopausal. It found no differences between the two groups, but the control women were slightly taller and with a lower body mass index (BMI); after correcting for weight, the results were lower in the FM group. In the same vein, another work\(^7\) analysed the BMD with US (calcaneum) and DXA (LS and distal forearm) in 40 premenopausal women with FM and 37 healthy women of the same age, and found no difference either by US or by DXA (BMD in LS, 1.248 g/cm² in FM vs 1.240 g/cm² in the controls). However, the BMD in the distal third of the forearm was lower in patients with FM (0.699 g/cm² vs 0.724 g/cm²; p= 0.02).

Other authors have evaluated the influence of risk factors, such as depression or physical activity, on the development of osteoporosis in these patients. Erdal et al.\(^8\) evaluated the BMD through DXA in the LS and FN in 38 women with FM and 20 healthy controls (25-50 years), determining also their level of depression with the Beck scale. The BMD was lower in the FM group with respect to the control group, both in the LS (DMO= 0.950 ± 9.902 vs 1.000 ± 6.082; p= 0.026) and in the FN (DMO 0.840 ± 0.123 vs 0.920 ± 7.654; p= 0.003), finding a negative correlation between Beck’s scale of depression and values of BMD in both locations (r= -0.53, p= 0.001 in LS; r= -0.47, p= 0.005 in FN) in all the women combined. Jensen et al.\(^9\) analysed BMD (using DXA in the LS and FN) in 31 women with FM (20 premenopausal and 11 postmenopausal) and 40 healthy women (30 premenopausal and 10 postmenopausal), applying, also, the VAS scale for pain and studying the degree of physical activity in daily life with FIQ. They found no differences in BMD in either of the two locations, although in the premenopausal women with FM the BMD in LS was correlated negatively with the degree of pain and the FIQ score (r= -0.52, p= 0.003; and r= -0.31; p= 0.09, respectively, from which the authors conclude that the severity of FM can have a negative impact on bone mass.

Another, older, work, and with a lower number of patients\(^10\), studied in 24 premenopausal women (12 with FM and 12 healthy) the BMD using DPA (dual photon absorptiometry) in LS and FN, as well as markers for bone remodelling in the blood (alkaline phosphatase and osteocalcin) and urine (calcium/creatinine and hydroxyproline). They found no differences either in bone mass or in markers for bone formation between the two groups, but they did observe that the calcium/creatinine quotients in urine were higher in the women with FM than in the control group (0.35 vs 0.19 mM/mM [p= 0.01] y 22 vs 12 µM/mM [p= 0.002], respectively), which appears to indicate an increase in bone resorption in these women. More recent studies have also failed to clarify the possible association between low BMD and FM. Ulusoy et al.\(^11\) found no differences in BMD in either the lumbar spine or the femoral neck, after an analysis of 30 women with FM and 30 healthy controls of the same age.

Other works have analysed markers for bone remodelling in patients with FM. Maghraoui et al.\(^12\) measured blood levels of osteocalcin, crosslaps (CTX) and parathyroid hormone (PTH) in 81 people (41 healthy, 40 with FM), finding that those patients with FM had blood levels of CTX and PTH lower than the control group, from which the authors conclude that the patients with FM had reduced bone resorption.

Conclusion
FM is a disease characterised by the presence of diffuse chronic pain, associated with other symptoms such as fatigue, depression or non-restorative sleep. This disease has risk factors in common with osteoporosis. Various works have analysed bone mass and levels of vitamin D in patients with FM, but the results are less than conclusive. In addition, most of these studies have been carried out with a low number of patients and with highly heterogeneous control groups. New works are needed which will analyse in depth the association between these two diseases.

Bibliography
10. Patten SB, Beck CA, Kassam A, Williams JV, Barbui C,


