Journal of Research and Practice on the Musculoskeletal System
JRPMS

Review Article

Association between fibromyalgia and osteoporosis

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Abstract

Fibromyalgia (FM) is a condition associated with chronic musculoskeletal pain, fatigue, joint rigidity, sleep interruption, depression and cerebral dysfunction. It is a complicated syndrome with not well-known pathogenesis and only clinical diagnosis at the present. Osteoporosis, however, is described as a skeletal disease, which main characteristics are: (1) reduced strength of the bone which is associated with the loss of skeletal mass and (2) micro-architectural deterioration of the bones, without clinical symptoms-except when fractures occur. In recent years, few studies have addressed the relation between fibromyalgia and osteoporosis. Most studies show that fibromyalgia may lead to an increased possibility of osteoporosis due to low levels of exercise because of the chronic pain. In addition, when Vitamin D levels are measured in patients with firbromyalgia syndrome it seems to be lower than general population. However, results of studies of the bone mineral density (BMD) of these patients are conflicted. In this short review article, we provide current knowledge on the relationship between fibromyalgia and osteoporosis, and in addition we discuss the association between fibromyalgia syndrome (FMS) and low bone mineral mass as shown in previously published papers including for systemic reviews and meta-analysis on these subjects.

Keywords: Bone mineral density, Chronic pain, Fibromyalgia, Osteoporosis, Vitamin D

Introduction

Fibromyalgia is a complicated syndrome. Despite the fact that its pathology is not well understood[1] yet it seems to be quite common in the general population as it has been shown to reach a prevalence worldwide about 2-3%[2]. It affects the muscles and it is associated with hypersensitivity to external painful stimuli , such as pressure(ischemic or mechanical) and change of temperature (heat or cold). The more common clinical features include hyperalgesia, chronic pain which cannot be controlled with common painkillers, high rates of depression, anxiety, sleep alterations and interruption, mood disorders and other psychiatric disorders, cognitive dysfunction and joint stiffness[3].

In general, fibromyalgia is a pathological entity which is observed in all ages, sexes and ethnicities with a possible genetic background which, however, as a fact is still being under discussion with multiple researches try to determine its pathology. Fibromyalgia is more common in women than in men (ratio of 10:1)[4]. Fibromyalgia is a rheumatological disorder which is quite common, affecting 2-8% of the general population (that always depends on the criteria used to diagnose the disease)[5]. It belongs to a group of disorders termed the affective spectrum disorders (ASD). These disorders can be observed either to individuals or families and have a genetic risk of expression of the symptoms. In addition to fibromyalgia the most common and well-known ASD's are (1) hyperactivity/attention-deficit disorder, (2) major depressive disorder, (3) migraine, (4) anxiety disorder, (5) cataplexy, (6) obsessive compulsive disorder, (7) bulimia nervosa, (8) panic disorder, (9) social phobia, (10) premenstrual dysphoric disorder, (11) posttraumatic stress disorder, and (12) medical disorders such as irritable bowel syndrome[6].

The prevalence of the disease increases with age, but

The author has no conflict of interest.

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Edited by: *Konstantinos Stathopoulos*

Accepted *19 November 2023*

is most often observed between adults (between ages of 20 and 55). As we mentioned, most typical symptom of the disease includes diffuse pain, which most often leads the patient to seek medical help and often there are other unexplained symptoms such as anxiety, major depression disorder and functional impairment of daily activities. It commonly affects both sides of human body and, in terms of the clinical examination, there are described some tender points, as specific regions in the body with high tenderness which are typically found in patients affected by FMS. There are 18 tenderness points (2 points given in each side of the body). The diagnosis of Fibromyalgia includes two variables (according to the American College of Rheumatology-ACR-): (1) chronic widespread pain that lasts constantly for more than three months characterized by pain at least at 11 of these tender points[1]:

I. Occiput → at the insertions of the suboccipital muscle just at the base of the human skull

II. Low cervical vertebrae → at the anterior aspects of the intertransverse level between 5th and 7th cervical vertebrae

III. Trapezium → at the spot where the back muscles attach to the shoulder just at the middle trapezius (the upper muscular border)

IV. Supraspinatus → above the acromion near the middle border of the scapular boner

V. Ribs → on the right and left side of the sternum just next to the second costochondral junction and about 2 inches below the collar bone

VI. Elbow → 2 cm distal to the epicondyle of each elbow just next to the lateral epicondyle

VII. Great Gluteal Muscle → in upper outer quadrants of each buttock

VIII. Femur → Just to the area of the tip of great trochanteric of each femoral bone

IX. Knee joint → at the medial fat pad proximal to the joint line

(2) Generalized pain, and (3) no other disorder that could explain the symptoms[1].

Despite the fact that there are high levels of pain described by the patients, there is no tissue damage or inflammation or any type of deformity associated with the syndrome. The pathophysiology of the disease remains undefined, though it is probably multifactorial including abnormal cortical processing in the brain, reductions in inhibitory pain modulatory mechanisms and molecular changes to the pain pathways. Studies have shown that patients who suffer from fibromyalgia compared with healthy controls need 50% lower stimulis to response in pain[4,6].

Reactive Oxygen Species (ROS) seem to be produced in higher levels in patients with Fibromyalgia than healthy population and their antioxidant ability is decreased, if contributed to situations of oxidative stress[4]. The central nervous system is highly susceptible to ROS because of its high lipid content (compared with other body parts)[4]. It is possible that the expression and also progression of the disease depend on abnormally increased levels of Reactive Oxygen Species (ROS)[7]. It is suggested that using vitamins and antioxidants as treatment of Fibromyalgia Syndrome (FM) (in addition with drugs such as antidepressants and pregabalin) possibly could change the florid psychotic symptoms of the patients[1]. Unfortunately, there is no specific treatment for Fibromyalgia until now, and for the majority of the patients the treatments used can cause temporary beneficial results or reduced efficiency of the treatment in order to improve the patients' symptoms. Drugs used include antidepressants (such as SSRI's-selective serotonin reuptake inhibitors - SNRI's - norepinephrine/serotonin reuptake inhibitors - and TKA - tricyclic antidepressants), pregabalin (an anti-epileptic drug which seem to help with widespread pain), painkillers such as Non-steroidal anti-inflammatory drugs (NSAIDs) or opioids and also some pharmaceutical investigational agents[1,2]. There are suggested also many non-pharmacologic treatments, including exercise, massage therapy, physiotherapy, specific diet and acupuncture, but the evidence of their use are controversial[2]. The fact is that despite that Fibromyalgia greatly limits the daily life of the patiets and deteriorates quality of life, it is not a life-threatening disease[4].

On the other hand, osteoporosis is a disorder which is characterized by decreased bone mass and microarchitectural deterioration which may lead to bone fragility and low energy fractures[8]. There are two main types of osteoporosis: primary and secondary. Primary osteoporosis is the most common and it is related with age process and decreasing sex hormones. It includes the postmenopausal osteoporosis - which is the most common - (type I osteoporosis) and the senile osteoporosis (type II osteoporosis). Postmenopausal osteoporosis is associated with decreased levels of of estrogen and it is resulting in increased bone turnover, where during bone remodeling resorption exceeds formation and also there is initial loss of trabecular bone followed by lose of cortical bone. Type II osteoporosis is common in both sexes and represents the gradual age-related bone loss caused by systemic factors, and it is induced by the loss of stem-cell precursors, with a predominant loss of bone (especially cortical bone). In secondary osteoporosis there is a factor or disease which is associated with bone lose such us hyperthyroidism, Cushing disease, hemato-oncological diseases, metabolic disorders or even some drugs[9]. Many researches are associated with the pathogenetic factors of osteoporosis and biological markers as an additional tool to assess anti-osteoporosis efficacy, predict osteoporotic fracture risk and indicate the causes of osteoporosis[10].

Despite the fact that fibromyalgia and osteoporosis appear to present via different pathways, a number of researchers have tried to establish a possible connection between these entities. In our review we attempt to study the researches about fibromyalgia which are focused on molecular factors and mechanisms related to bone metabolism and bone biochemistry which could be possibly

associated with the disease[1,11]. In addition, low body exercise and functional impairment of daily activities may cause lower BMD, and higher possibility of osteoporosis. Furthermore, a number of studies have associated fibromyalgia with low levels of Vitamin D, a vitamin with pleiotropic actions related to calcium and phosphorus homeostasis, cell differentiation, immune response, intermediary metabolism, bone metabolism and also the cardiovascular system[12]. Based on the published studies, in our article we are trying to see if there is any association between fibromyalgia syndrome and osteoporosis.

Methodology

We used PubMed as a database for our internet research. We searched only for English-language articles where an association between osteoporosis and factors and fibromyalgia was reviewed. We used fibromyalgia, osteoporosis and Vitamin D as keywords to our research. Articles written in other languages; clinical trials were excluded. Also, articles with patients with diseases which cause chronic pain, arthritis and osteoporosis were excluded. Based on the inclusion and exclusion criteria, we selected only randomized controlled studies and systematic reviews that regarding the association between fibromyalgia syndrome and osteoporosis or Vitamin D levels.

Results

In total we found 255 results through our research. Only 11 from them met the criteria ofour research and were used to extract information for our article[13-23].

Studies in favor of association between osteoporosis and fibromyalgia

The association between levels of bone mineral density (BMD) as a link between fibromyalgia and osteoporosis constitutes the target of many studies[13-16]. A study in the Rheumatology Unit at Ninewells Hospital which tried to determine if women patients with fibromyalgia are in higher risk of developing osteomalacia or osteoporosis demonstrated several interesting findings. Patients' age was between 35 and 50 years, and only premenopausal women were included (40 patients with fibromyalgia and 37 healthy controls). All the patients were tested by performing bone mineral density tests (using DXA technique and Ultrasound) and checked for fibromyalgia tenderness spots in the clinical examination. In addition, blood tests were done checking the levels of Vitamin D, Calcium, γ-gt, plasma viscosity, PTH and ALP. The results of this study were very interesting. Using several scales for estimating functional impairment and mobility, patients with Fibromyalgia had significant functionality in contrast to healthy controls. In addition, researchers observed more tenderness points and sleep disorders in these patients. As long as the laboratory findings are concerned, the most significant finding was the proportion of low levels of Vitamin D - levels lower than 20 nmol/l - (45% of patients with fibromyalgia versus 19% of control group). No significant differences were measured within levels of PTH and Calcium. The other biochemical factors (γ-gt, plasma viscosity and ALP) were calculated within normal limits but it was observed that those limits in patients with fibromyalgia were within the higher normal levels. As long as the Bone Mineral Density's results are concerned, significantly lower levels were observed only in the mid-distal radius of patients with fibromyalgia. 14 patients with fibromyalgia had history of previous fracture (35%). On the other hand only 5 healthy controls had experienced a fracture in the past (16.2%). Despite the fact that this study shows an association between patients with fibromyalgia and osteoporosis we must take under consideration that in this research they were included only premenopausal women[13].

Another study, which was carried out in University of California tried to investigate if there is any association between osteoporosis as defined by low levels of BMD in healthy controls and patients with Fibromyalgia Syndrome. The Rheumatology criteria for FM by the American college were used. Bone Mineral Density of Femoral Neck and Spine were evaluated. This study included 24 women patients with fibromyalgia aged from 33 to 60 years and 24 healthy controls of similar age (+/- 3 years) and ethnicity. There were 3 groups based on their age (31-40 year, 41-50 year and 51-60 year). All patients with Fibromyalgia had lower levels of BMD of the spine and femoral neck using simple T test. The patients with Fibromyalgia in all 3 groups had a lower mean BMD of the spine and the difference was statistically significant. The femoral neck BMD was also lower, but not significant (except for patients of the 51-60 age group where the difference was statistically significant). Only BMD differences were tested in this study. Blood tests were not included[14].

One large recent research, used the largest Israel's database to address the co-existence of osteoporosis with fibromyalgia. 14,296 patients with and 71,324 sex- and age-matched controls were chosen. Body mass was tested in each patient. Data were analyzed using chi-square and t-tests. About 17% of the patients with fibromyalgia were osteoporotic. In contrast, in control group this proportion was 12% showing that Fibromyalgia possibly could be a risk factor of development of osteoporosis[15].

Moreover, scientists who researched the relation between BMD and Fibromyalgia through a cross sectional study carried out on people with Fibromyalgia of unknown sex and age in South India using VAS and FIQ. This study included totally 158 patients attending camps in rural areas of South India. Between the people that were screened low BMD was seen in 129 people (81.6%) and only a percentage of 23,4% (37 people) was diagnosed with Fibromyalgia. From these patients with FMS a percentage of 83.7% had low BMD (31 of 37 patients) and 98 of 121 people (80,9%)

who were no diagnosed with FMS. Furthermore, patients with FMS and low BMD had higher levels of pain[16].

Association of biochemical markers

As already discussed, there are a few studies which try to indicate if there is an association between pathological levels of vitamins or biochemical markers and Fibromyalgia. Vitamin D levels in terms of co-existence with fibromyalgia have been studied in numerous publications. In general, studies which are evaluating if there is association between vitamin D and fibromyalgia are controversial. A meta-analysis designed based on PRISMA guidelines tries to indicate if there is any association between vitamin D and fibromyalgia[30]. As we know Vitamin D is important for immune system of the human body and it is related with many autoimmune disorders such as rheumatoid arteritis, multiple sclerosis (MS), mellitus, diabetes type I (Insulin depended) and irritable bowel syndrome (IBS). Reference to deficiency of Vitamin D is defined as levels of serum level of 25 hydroxy vitamin D (25-OH-Vitamin D) lower than 20 ng/ml (50 nmol/ml). There are many people worldwide who suffer from Vitamin D deficiency (it is suspected that there are more than one billion people). This problem especially in patients where levels of Vitamin D are lower than 10 ng/ml can cause symptoms such as proximal muscle weakness, skeletal mineralization insufficiency, higher risk of falling in the elderly, and widespread body pain symptoms that are either common with fibromyalgia or osteoporosis (as we know low level of Vitamin D are associated with osteoporosis and the base of osteoporosis' treatment are Vitamin D supplements). This meta-analysis[30] uses 12 studies out of 1579 found in the databases (included studies were case controls carried between 2009 and 2016 and including women patients and healthy controls)[17-29]. All studies were carried out among 851 patients with Fibromyalgia and 862 healthy controls. In eight studies, the level of 25-OH-Vitamin D was lower in patients than healthy controls. Six of those eight studies reported statistically significant results. The rest four studies out of twelve reported higher levels of 25-OH-Vitamin D, but only one of the differences had statistical significance[30].

A study in the Rheumatology Unit at Ninewells Hospital, as already discussed, examined many factors between FMS patients and healthy controls including biochemical markers (of Vitamin D, Calcium, γ-gt, plasma viscosity, PTH and ALP). No significant differences were measured within levels of PTH and Calcium. Levels γ-gt, plasma viscosity and ALP were in the higher normal limits of the patients with fibromyalgia. Three out of 23 people with fibromyalgia (7.5% of all the patients with Fibromyalgia and 16.7% of those with low serum 25-OH vitamin D) and just one of 31 control people were diagnosed with biochemical osteomalacia, defined by raised serum levels of parathyroid hormone (PTH) with normal level of Calcium (Ca). As long as Vitamin D is concerned, this study showed that there is an important high number of patients with low levels of serum Vitamin D (18 patients -45%- versus 7 healthy controls -18.9%). Despite that fact, there were no significant differences in the parameters studied between patients with Fibromyalgia with low serum of vitamin D (<20 nmol/l) and those with higher levels of Vitamin D (≥20 nmol/l) [Although the levels of serum PTH were found to be higher in patients with lower serum levels of Vitamin D, the difference was not statistically significant][13].

One other study which was done was done at Medical OPD of Civil Hospital Karachi between female patients were used for this study diagnosed using criteria for Fibromyalgia according to ACR. Only 40 patients were included to the study. All of them were women and the mean age was 37.65 +/-11.5 years. Normal blood CP, ESR, Ca, P and ALP and luck of systemic disease were a necessary condition so that they were included to the study. This study showed that the 80% of the patients had Vitamin D deficiency and the 20% insufficiency. Despite there was a small sample it is noticeable that none of them had sufficient levels of Vitamin D[31].

Parathormone (PTH) is an other hormone associated with bone turnover which is studied knowing that hyperparathyroidism and Fibromyalgia may present with similar symptoms (anxiety, lose of weight, widespread pain, insomnia, depression) and it is a risk factor of osteoporosis[12].

A cross sectional study occurred by University Feneral de Pernambuco in Brazil between 100 patients with fibromyalgia and 57 healthy controls aged 20–55-year. FM group met criteria for Fibromyalgia according to the ACR - criteria of both classification and diagnosis. Only women were used in this study. Patients excluded if they suffered of systemic disease or were in replacement therapy with Vitamin D or/and Calcium. PTH, Ca and albumin levels were calculated, as well as symptoms of the patients who belonged in Fibromyalgia Group. Based on the criteria for diagnosis of hypercalcemic hyperparathyroidism, through the study six patients with fibromyalgia were diagnosed (6% frequency). No person in the comparison group had been diagnosed with PHP (despite that fact the difference was not statistically significant). However, the frequency of hyperparathyroidism with normal calcium levels in patients with fibromyalgia was 17% versus 5.2% in the group of healthy controls (fact with statistical significance). In general showed that although Calcium levels were normal, PTH levels had been significantly higher than in the control group resulting that hyperparathyroidism was more frequent in people with fibromyalgia[32].

Studies against the association between osteoporosis (and/or low levels of Vitamin D) and fibromyalgia

Despite the fact that many studies indicate an association between osteoporosis and fibromyalgia[13-16,30-32], not all the studies showed association between fibromyalgia and

osteoporosis or risk factors which may result osteoporosis or osteomalacia. For example, a cross linked study which was occurred at the Outpatient Clinic of Joao Pereira dos Santos Rheumatology Polyclinic in Barbalha County, Ceara State, Northeastern Brazil between Fibromyalgia patients and healthy controls did not show correlation between Fibromyalgia and levels of Vitamin D that had a statistical significance. To this study there were compared 40 individuals and 43 patients with fibromyalgia (based on ACR 2010 criteria) aged between 18 and 60 years (81 females and two males - one in each group). Individuals with systemic disease or people who were taking Vitamin D supplements were excludes. Vitamin D was measured in all the participants. Also in patients with fibromyalgia Ca, Alb, P and PTH were tested. All Fibromyalgia had symptoms of widespread pain based on the VAS scale (3 out of 4 presented severe levels of pain and the rest of them -25%- had moderate pain). Totally, almost have of the patients with severe pain (45.4%) had vitamin D levels lower than 30 ng/mL, when only 9% of them had levels of serum Vitamin D lower than 20 ng/mL (fact with not statistical significance). In addition, there was difference in levels of vitamin D between the two groups of patients with fibromyalgia and healthy controls but with no statistical significance. Only a small percentage of the patients (about 4.8%) had serum vitamin D deficiency levels, whereas there was no individual in the control group with such deficiency. No patient presented severe vitamin D deficiency (<10 μg/mL)[33].

Furthermore, there was a cross-sectional study at Gaziomanpasa University in Turkey between 30 women with fibromyalgia and 30 aged-matched healthy controls. In this study, BMD values and levels of some biochemical markers (25-OH-Vitamin D, PTH, ALP, Ca, P) were measured. Although that levels of Parathormone were higher in patients with Fibromyalgia there was no difference in the levels of serum 25-OH-Vitamin D or BMD - both measures in femoral neck and lumbar spine-with statistical significance. There was not also relation between levels of Vitamin D and pain levels (VAS, FIQ and HADS score)[34].

Meta-analysis

Finally, there are few meta-analyses about fibromyalgia and osteoporosis. The results are in general conflicted. It is an interesting finding that in two meta-analysis it was observed that patients with fibromyalgia syndrome have lower levels of Bone Mineral Density in lumbar spine but not in femoral neck as long as lower levels of Vitamin D[35,36].

For example, a meta-analysis by Sikarin Upala, Wai Chung Yong and Anawin Sanguankeo used MEDLINE and EMBASE databases to see if the decreased BMD and fibromyalgia are associated. Four observational studies were included in the analysis. Criteria of ACR were used for the diagnosis of Fibromyalgia. DXA was the chosen method used to measure the BMD of the femoral neck and the lumbar spine (L2-L4). Data involved 680 individuals. It was observed that there was statistically significant decreased lumbar BMD in the patients of fibromyalgia compared with healthy controls. As long as the BMD in femoral neck is concerned there was not observed statistical significance difference between the two groups[35].

In conclusion, a meta-analysis by Young Ho Lee and Gwan Gyu Song aimed to evaluate if there is any association between fibromyalgia and osteoporosis based on BMD. They were compared FM patients and healthy individuals but also there was comparison between patients with fibromyalgia in subgroups (based on ethnicity, age, sex and BMD). There were used twelve studies, including 784 healthy and 695 patients controls to compare and extract results. The BMD measurement showed that patients with fibromyalgia had statistically significant lower BMD than control individuals with DXA method and dual-photon absorptiometry but not by quantitative ultrasound. Meta-analysis showed a significantly lower BMD levels in the group of Fibromyalgia patients in Caucasian populations than in Turkish populations. In addition, subgroup analysis using criteria of the age, sex and menopause status, menopause status showed a statistically significant lower measurement of BMD in the women patients with Fibromyalgia but not in the pre-menopausal group and the group with individuals aged greater than mean age 50 years old. Finally, this meta-analysis demonstrated that levels of BMD was lower (statistically significant) in Fibromyalgia patients in Caucasian and women[36].

Conclusion

Fibromyalgia is a relatively new medical condition, and the causes and pathogenetic factors of this syndrome are not yet well defined. Most studies are trying to indicate the association between fibromyalgia and others rheumatological disorders or psychiatric conditions. As long as the association between fibromyalgia and bone health is a new field of researches, studies are not many and the results are in many of them contradictory. In addition, we have to signalize that most of the studies used a small percentage of patients. This small sample size in addition to the high heterogeny and the small studies through many different regions of the world where the population has different characteristics, may lead to doubtful results. In the future, more studies may lead to objective results which could clarify the etiopathogenesis of Fibromyalgia Syndrome, and the association between Fibromyalgia and osteoporosis aiming to the prevention of many symptoms and the demarcation of suitable and necessary therapeutic targets.

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