A case-control analysis of the associations between Fibromyalgia Syndrome and Osteoporosis

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ABSTRACT **Background:** Fibromyalgia syndrome (FMS) is characterized by widespread musculoskeletal pain and tenderness with associated neuropsychological symptoms such as fatigue, unrefreshing sleep, cognitive dysfunction, anxiety, and depression. Osteoporosis is defined as a reduction of bone density. Previous studies to determine an association of FMS with osteoporosis showed mixed results, partially due to small sample sizes and lack of statistical power.

Objectives: To evaluate the association of FMS with osteoporosis.

Methods: We conducted a case-control study utilizing the database from Israel's largest health maintenance organization. FMS patients were compared to age- and sex-matched controls. Data were analyzed using chi-square and *t*-tests. Multivariable logistic regression models assessed the association between osteoporosis and FMS. Spearman's rho test was used for correlation.

Results: We utilized data from 14,296 FMS patients and 71,324 age- and sex-matched controls. Spearman's rho test showed a significant correlation between FMS and osteoporosis (correlation coefficient 0.55, $P < 0.001$). A logistic regression for osteoporosis showed an odds ratio [OR] of 1.94 (95% confidence interval [95%CI] 1.83–2.06, $P < 0.001$) for FMS compared to controls and found higher body mass index to be slight protective (OR 0.926, 95%CI 0.92–0.93, $P < 0.001$).

Conclusions: There is a significant correlation between FMS and osteoporosis. Early detection of predisposing factors for osteoporosis in FMS patients and implementation of suitable treatments and prevention measures (such as dietary supplements, resistance or weight bearing exercise, and bone-mineral enhancing pharmacological therapy) may reduce both occurrence rate and severity of osteoporosis and its complications, such as fractures.

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The fibromyalgia syndrome (FMS) is a chronic widespread pain syndrome characterized by tenderness and diffuse stiffness commonly accompanied by mood, cognitive, fatigue and sleep disturbances, and functional impairments [1]. The prevalence of FMS in the general population is estimated to be 2% to 4% [2,3], with female predominance of 1:5 to 1:9 in most population-based studies and with a peak prevalence in people over age 40 years [3,4]. The pathogenesis of FMS is believed to be multifactorial with familial, genetic, environmental, endocrine, and neurological factors playing a seminal role [5]. Non-modifiable risk factors associated with FMS are age, sex, cultural and ethnical background, genetics, socioeconomical status (SES), and a history of trauma (both physical and mental, with sexual trauma as major contributors).

Osteoporosis is defined as a decrease in bone density and strength, usually clinically tested by dual-energy X-ray absorptiometry (DEXA) test. The loss of bone tissue is related to weakened skeletal architecture. Osteoporosis prevalence increases with age with a prevalence rate of 5.9–7.2% in men and 19.1–23.5% in women over the age of 50 years. The sex difference is attributed mainly to the postmenopausal period (loss of ovarian function in females) at around age 50 years, which triggers a rapid bone loss cascade). The main risk in osteoporosis is its related fractures causing major damage including disability, loss of quality of life, medical costs, and death [6,7] with deaths and morbidity due to osteoporotic fractures outnumbering those of all types of cancers (excluding lung cancer) [8].

Factors associated with low bone mass include age, female sex (in the postmenopausal period), low serum calcium and/or vitamin D levels, smoking, sedentary lifestyle, and other genetic acquired and environmental factors [7].

Numerous studies have examined the association between FMS and other diseases, particularly in the psychiatric and rheumatic spectrum. In contrast, the link between bone density, osteoporosis, vitamin D, and chronic pain syndromes is a topic that has been hardly researched. Studies performed over the past two decades make it clear that further research in this area is needed.

In this study, we evaluated the association of FMS with os-

teoporosis using the clinical database of Clalit Health Services, the largest healthcare organization in Israel.

PATIENTS AND METHODS

We conducted a population-based case-control study using data from Clalit. This health fund has a comprehensive, electronic database with continuous, real-time input integrating information derived from pharmaceutical, medical, and administrative systems.

Clalit provides services to a population of approximately 4,500,000 members. The Clalit database enables researchers to evaluate real-life populations on a large scale, including outpatients and inpatients in primary, secondary, and tertiary care centers. In the Clalit database, the diagnoses of chronic diseases are based on data derived from hospital and community-based physician records. These diagnoses are validated systematically using logistic checks (such as comparing diagnoses from various providers). The database undergoes routine manual analysis and validation to ensure its accuracy.

RESEARCH VARIABLES

Patients were defined as having FMS or osteoporosis when their medical records contained at least one diagnosis by a relevant physician (e.g., rheumatologist, pain specialist for FMS), ICD-9 code, or other relevant criteria predetermined the Clalit, including a specific osteoporosis registry.

All FMS patients in the Clalit database were included in the FMS group. Controls were randomly selected from the general population in Clalit. The data file is structured so that each FMS patient had five sex- and age-matched controls.

Independent variables included sex, age (at the time the file was produced), SES (according to the clinic address/residential address in the HMO database), smoking status (present or past according to ICD-9 code), body mass index (BMI) according to the medical file, and diagnoses of osteoporosis and FMS.

Data were analyzed using the chi-square test for categorical variables and Student's *t*-test for continuous variables. Multivariate logistic regression model to assess for the association between osteoporosis and FMS was performed as well as Spearman's rho test for correlation.

The study was approved by the Clalit Health Services Ethics Committee, located at Soroka Medical Center, Beer Sheva, Israel.

RESULTS

The study included 14,296 FMS patients and 71,324 age- and sex-matched controls. Descriptive characteristics for these groups are shown in Table 1. Mean age of FMS patients and controls was approximately 55.5 years of age, with a female predominance of 92.4%. FMS patients were more likely to be at a lower SES compared to controls, and smoking was more prevalent among the FMS patients. In the independent t-test analysis, Levene's test for equality of variances was non-significant for age (F=2.685, $P = 0.101$) and significant for BMI (F=36.842, $P < 0.001$). The *t*-test for both age and BMI were significant ($t = 6.071$, $P < 0.001$; $t = -20.016$, $P < 0.001$, respectively). BMI, which was not part of the data matching, was significantly higher in the FMS group compared to controls with a mean of 29.11 kg/m^2 compared to 27.97 kg/m^2, respectively). An association was observed between FMS and SES (chi square 424.703, $P < 0.001$), FMS and smoking status (chi square 128.630, $P < 0.001$), and FMS and osteoporosis (chi square 256.029, $P < 0.001$).

Table 1. Descriptive characteristics of the study population (n=85,620)

Characteristics	Fibromyalgia N=14,296	No fibromyalgia N=71,324
Age in,years, mean ± standard deviation	55.25 ± 13.88	56.01 ± 13.74
Female sex, n (%)	13,210 (92.4%)	65,910 (92.4%)
Body mass index, kg/m^2, mean ± standard deviation	29.11 ± 6.20	27.97 ± 6.01
Smoking, n (%)	4,679 (32.7%)	19,987 (28.0%)
Socioeconomic status*		
Low, n (%)	6669 (46.8%)	27,747 (39.2%)
Medium, n (%)	5397 (37.9%)	27,499 (38.8%)
High, n (%)	2182 (15.3%)	15,554 (22.0%)
Osteoporosis, n (%)	2424 (17.0%)	8592 (12.0%)

*572 cases did not have socioeconomic status, data shown is valid percent

In the FMS group 2424 patients (17.0%) were found to have co-morbid osteoporosis compared to only 8592 patients (12.0%) in the control group. Spearman's rho test for correlation showed a significant correlation between FMS and osteoporosis (correlation coefficient 0.55, $P < 0.001$).

Furthermore, we performed a logistic regression for osteoporosis as a dependent variable by sex, age, SES, BMI, smoking status, and FMS status. A high SES was not significant in this equation. As expected, female sex has an osteoporosis of 9.377 (95% confidence interval [95%CI] 7.76–11.33, $P < 0.001$). FMS had an osteoporosis of 1.94 (95%CI 1.83–2.06, $P < 0.001$). Higher BMI was the only parameter of a protective value, although minor, with an odds ratio of 0.926 95%CI 0.92–0.93, $P < 0.001$). Overall, the model explains 32.1% of osteoporosis variation [Table 2].

Table 2. Logistic regression model of analysis of risk factors for osteoporosis in the study population (n=85,620)

Variable	B	WALD	Odds ratio (95% confidence interval)	*P* value
Age, years	0.111	9582.994	1.12 (1.115–1.120)	**< 0.001**
Female sex	2.238	540.024	9.38 (7.764–11.325)	**< 0.001**
Body mass index, kg/m²	-0.077	1112.388	0.93 (0.922–0.0.930)	**< 0.001**
Smoking history	0.088	11.073	1.09 (1.037–1.150)	**0.001**
Socioeconomic status				
Low	–	9.704	–	**< 0.008**
Medium	0.084	9.675	1.09 (1.088–1.032)	**< 0.002**
High	0.043	1.840	1.044 (0.981–1.112)	**0.175**
Fibromyalgia	0.663	507.734	1.94 (1.831–2.055)	**< 0.001**
Constant	-8.970	4392.703	0.000	**0.000**

Omnibus tests of the model coefficients indicated that the chi-square of the model is 15728.85 with significance of < 0.001

Nagelkerke R square is 32.1% (0.321)

DISCUSSION

This population-based, case-control study was designed to investigate the association between FMS and osteoporosis. Our results demonstrated a correlation between both conditions and showed FMS as a risk factor for osteoporosis.

Most studies that have dealt with this association have shown contradictory results. In addition, no clear biological mechanism has been demonstrated so far [9-16]. Possible explanations allude to the impact depression, musculoskeletal pain, fatigue, pain, and other mental or physical symptoms of FMS have leading to a sedentary life style with decreased sun exposure and low levels of serum vitamin D. FMS is also associated with various other chronic diseases, such as irritable bowel syndrome, which might be related to a reduced intake of nutrients and vitamins (in part due to avoidance of calcium-rich dairy foods), and a consequent deterioration of overall health and of bone strength in particular. It has been well established that vitamin D is relevant not only in calcium homeostasis, but may also play a role in pain pathways, brain function and in the inflammatory response [17-19].

Several characteristics of FMS patients should have been protective against osteoporosis. It has been shown that patients presenting with chronic pain syndromes in general and FMS specifically attend more medical appointments, perform more medical examinations, and are treated with more medications [20,21]. These findings may help to diagnose osteopenia earlier. However, these results can create an overdiagnosis bias in the FMS group with patients unnecessary being classified as having osteoporosis despite minimal risk factors.

A number of meta-analysis and systematic review reports addressed this issue [9-13,15,16]. Lee and Song [9] reviewed 12 articles (695 FMS patients, 784 controls) and showed significantly lower bone density in FMS patients, particularly in Caucasian women primarily in their lumbar spine (rather than the femur). However, the authors emphasized that most studies included a small sample size, lacked adequate statistical power, and were highly heterogeneous, involving different regions of the world (i.e., different sun exposure profiles) and did not address confounders.

Studies regarding the association of FMS and pain levels with vitamin D concentration (low serum levels or dietary supplement use) are inconclusive [10-12,16,22,23]. Joustra and colleagues [12] examined the literature regarding vitamin and mineral deficiency in chronic fatigue syndrome and FMS. Their meta-analysis included 27 studies and showed no significant difference in vitamin D or calcium serum levels between FMS patients and controls. Ellis et al. [10] presented mixed results in their systematic review on the role of vitamin D in FMS with an interesting observation showing a statistically significant summer increase in vitamin D levels in controls compared to FMS.

Randomized controlled trials (RCTs) dealing with this topic are limited [17,23,24]. In a double-blinded controlled trial in which 50 women with chronic diffuse pain and low levels of vitamin D were divided into a treatment group (weekly oral vitamin D) and a placebo. The researchers revealed no significant difference in pain levels after 3 months despite an increase in vitamin D levels in the treatment group [23]. However, a RCT by Mirzaei et al. [24] on the effect of vitamin D intake in 74 FMS patients with low levels of vitamin D showed that vitamin D supplements improved quality of life.

Gendelman et al. [17] conducted a double-blinded trial in patients presenting with musculoskeletal pain. Their trial showed that those who received vitamin D treatment compared to a placebo presented with a significant decrease in pain index (according to the VAS scale), a significant decrease in the use of SOS analgesics and a decrease in the concentrations of the proinflammatory cytokine TNFα, which is linked to pain mediation in many mechanisms as well as a decrease in the levels of PGE2 (whereas in the placebo group their concentrations increased).

In the Israeli population, Tandeter and colleagues [14] conducted a case-control study of 68 FMS patients and 82 controls. No significant difference was found between the groups with respect to serum levels of vitamin D. Seasonal changes in vitamin D levels were observed but these were not statistically significant.

LIMITATIONS

The lack of standardization for osteoporosis and FMS diagnosis is our main limitation. The database is created as a registry for medical record and not for research, thus tracing the diagnosis

origin or criteria used for each individual (approximately 85,000 patients) is impossible. This fact can contribute to a misclassification error, nevertheless the massive sample size was found to mask occasional errors such as this.

FMS is a controversial disease among rheumatologists with characteristics that can be considered stereotypical toward overdiagnosis or underdiagnosis in different populations. Thus, a choice bias may have occurred that affected the pooled data obtained including female:male ratio, age of diagnosis, co-morbidities, and more. In addition, it is possible that a differential classification bias also confounded our results, that is, ill patients tend to be seen by medical personal more often, and therefore are exposed to overdiagnosis, including the diseases studied.

The analysis chosen for this research was a standard unconditional analysis despite the data being sex and age matched. The literature approves unconditional analysis for non-individually matched groups as this step is simpler to perform and often yields better statistical outcome with no loss of validity. The disadvantages of not performing a matched analysis are considered negligible in such cases [25].

The main strength of this study is its large sample size. The Clalit database includes half of the country's population and represents the general population. The database includes outpatients and inpatients in primary, secondary, and tertiary care centers from all geographical and regions and SES strata.

CONCLUSIONS

There is a significant correlation between FMS and osteoporosis. Early detection of predisposing factors for osteoporosis in FMS patients and implementation of suitable treatments and prevention measures may reduce both occurrence rate and severity of osteoporosis and its complications, such as fractures.

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