Prevalence and clinical impact of fibromyalgia in patients with primary Sjögren's syndrome

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ABSTRACT

Objectives. *Clinical features of primary Sjögren's syndrome (pSS) overlap with those of fibromyalgia (FM). This cross-sectional study was conducted to investigate the prevalence of FM in pSS patients and to compare the clinical features of pSS patients with FM to those without FM.*

Methods. *One hundred pSS patients were consecutively assessed to identify the presence of FM according to the American College of Rheumatology (ACR) 2010 criteria. Clinical and laboratory data were collected from all patients. Additional assessments included EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) and EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI). The severity of depression was measured by Hamilton depression rating scale 17-items (HAM-D scale).*

Results. *The prevalence of FM was 31.0% (31/100) in pSS. Widespread pain index and symptom severity scale were significantly correlated with ESSPRI ($r=0.6542$ and $r=0.7173$, both $p<0.0001$) and HAM-D scale ($r=0.6734$ and $r=0.6471$, both $p<0.0001$) in pSS. In multivariate analysis, ESSPRI and HAM-D scale were independently associated with increase of tender point count and symptom severity scale. ESSPRI was significantly higher in pSS patients with FM compared to those without FM ($p<0.0001$). The prevalence of FM in pSS patients with moderate-to-severe depression was significantly higher than those with mild depression or without depression (odds ratio= 10.62, $p=0.0009$). Serum 25-hydroxy vitamin D3 levels in pSS patients with FM were significantly ($p=0.0072$) decreased compared to those without FM.*

Conclusion. *Our study showed that FM was prevalent in pSS. FM was associated with higher ESSPRI and more severe depression.*

Introduction

Sjögren's syndrome, characterised by lymphocytic infiltration of exocrine glands resulting in xerostomia and keratoconjunctivitis sicca, is a complex disease that may be accompanied by extra-glandular symptoms. In addition to ocular and oral dryness, chronic fatigue and somatic pain are frequent and disabling symptoms in patients with Sjögren's syndrome (1). Although end organ damage is uncommon in primary Sjögren's syndrome (pSS), pSS patients have considerable disability in all aspects of health (2). Despite an increasing interest in their fatigue and functional disability, the underlying pathogenesis of Sjögren's syndrome remains poorly understood.

Fibromyalgia (FM) is a common musculoskeletal pain disorder of unknown aetiology. Cardinal features of FM include chronic widespread body pain and hyperalgesia. FM may also exhibit a range of functional and emotional comorbidities, including fatigue, sleep disturbance, irritable bowel syndrome, headache, and mood disorders (3). FM can be often associated with other rheumatic conditions such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and pSS. In particular, FM and pSS tend to affect middle-aged women with several overlapping features. For instance, body ache, fatigue, and sicca symptoms are commonly reported. Although previous study has shown that fatigue in patients with Sjögren's syndrome is not due to coexistence of FM (4), the relationship between FM and pSS or clinical impact of concomitant FM in pSS is unclear.

There is no gold standard test for the diagnosis of FM. Most previous studies have used the American College of Rheumatology (ACR) 1990 criteria for the classification of FM, which are widespread pain of 3 months or more in combination with tenderness on pres-

sure (so called tender points) in at least 11 of 18 specified sites (5). The ACR preliminary diagnostic criteria for FM developed in 2010 did not require tender point exam. They focused on the extent of somatic symptoms. However, such criteria have not been tested in other rheumatic diseases (6). The objective of the present cross-sectional prospective study was to determine the prevalence of FM in pSS patients using the ACR 2010 criteria for FM and compare the clinical features of pSS patients with FM to those without FM.

Methods

A total of 100 pSS patients were consecutively assessed to identify the presence of FM based on the ACR 2010 diagnostic criteria (6). All patients met the American-European Consensus Group (AECG) criteria for pSS (7). Demographic and clinical characteristics of the 100 pSS patients are summarised in Table I. Patients known to have current thyroid dysfunction, infections, or any other chronic diseases were excluded from the study. The study was approved by the local ethical committee. Written informed consent was obtained from all participants.

Additional assessments included tender point counts, visual analogue scale (VAS) of pain and fatigue (0–100 mm), the Hamilton depression rating scale 17-items (HAM-D scale), and the presence of insomnia and cognitive dysfunction for all patients. The revised Fibromyalgia Impact Questionnaire (FIQR) was used for patients with concomitant FM (8, 9). Tender points were examined by two independent examiners according to the ACR 1990 criteria (5). The severity of depression in patients was classified into the following severity ranges based on the HAM-D scale: no depression (scale of 0–7); mild depression (scale of 8–16); moderate-to-severe depression (scale ≥17) (10). We calculated the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) to assess symptoms in pSS patients (11). We recorded the presence of insomnia and cognitive dysfunction. Insomnia was defined by the presence of a subjective report of difficulty with sleep that occurs despite adequate opportunity for sleep, and that results in some form of daytime impairment. Patient with insomnia was identified by using a positive response to either of two questions; "Do you experience difficulty sleeping?" or "Do you have difficulty falling or staying asleep?" and the sleep difficulty should occur at least 3 nights per week for 1 month or longer (12). Cognitive dysfunction was defined as an individual report of memory loss greater than expected for the individual's age and education level that interferes notably with activities of daily living, and that is happening more often or is getting worse during the past 12 months.

All patients underwent laboratory investigations including a complete blood count, erythrocyte sediment rate (ESR), C-reactive protein (CRP), the presence of antinuclear antibodies (ANA), anti-SSA/Ro, anti-SSB/La, rheumatoid factor (RF), levels of total serum immunoglobulin G (IgG) and complements (C3 and C4), serum β2-microglobulin, and serum 25-hydroxy vitamin D3 (25-(OH) Vit D3) levels. Disease activity in pSS was measured by using EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) (13).

Table I. Demographic and clinical characteristics of patients with primary Sjögren's syndrome (pSS).

	pSS (n=100)
Age (years)	54.3 ± 10.2*
Number of female (%)	97 (97.0)
Body mass index (kg/m^2)	21.8 ± 2.8
Disease duration (years)	8.1 ± 6.4
ESR (mm/h)	29.6 ± 24.1
CRP (mg/dL)	0.9 ± 3.5
RF positivity (%)	42 (52.5)
ANA (%)	71 (88.8)
Anti-SSA/Ro antibody (%)	74 (92.5)
Anti-SSB/La antibody (%)	52 (65.0)
Serum 25-(OH) Vit D3 (ng/mL)	26.7 ± 14.6
VAS of pain (0-100)	31.8 ± 29.2
VAS of fatigue (0-100)	45.6 ± 27.0
ESSPRI (0-10)	3.9 ± 2.6
ESSDAI (0-123)	1.6 ± 1.7
HAM-D scale (0-54)	9.4 ± 8.7

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor; ANA: antinuclear antibody; 25-(OH) Vit D3: 25-hydroxy vitamin D3; VAS: visual analogue scale; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; HAM-D scale: Hamilton-depression rating scale 17-items; *Mean ± SD.

Data were presented as mean ± standard deviation (SD) or median with interquartile range for normally and non-normally distributed data, respectively. Comparison of continuous data was performed using student's *t*-test or Mann-Whitney non-parametric U-test. Categorical variables were compared using chi-square or Fisher's exact test. Bivariate correlations were analysed by Pearson correlation coefficients. Associations between disease activity or severity of depression and the presence of FM (tender point counts, widespread pain index, and symptom severity scale) were further evaluated by linear regression analyses. The selection criterion for inclusion of test variables in adjusted linear regression analyses was set at $p<0.15$ in univariate analyses. Adjustments for known prognostic factors and other possible confounders including age, disease duration, CRP and 25-(OH) Vit D3 level, extraglandular manifestation, autoantibodies (anti-SSA/Ro and anti-SSB/La), ESSPRI, and ESSDAI were performed. All analyses were performed using PASW Statistics 18 (SPSS Inc., Chicago, IL, USA). Statistical significance was considered when a two-tailed *p*-value was less than 0.05.

Results

The prevalence of FM was 31.0% (31/100) in pSS patients based on the ACR 2010 criteria. However, the prevalence of FM tended to be lower when the ACR 1990 criteria were used (19.0% (19/100), $p=0.0718$). All FM patients who met the ACR 1990 criteria also met the ACR 2010 criteria, whereas 12 patients with concomitant FM only met the ACR 2010 criteria. Although these patients had VAS of pain or fatigue and FIQR scores similar to FM patients defined by the ACR 1990 criteria, they were older (59.7±7.5 *vs*. 52.1±10.6 years, $p=0.0317$) with higher symptom severity scale (9.75±2.24 vs. 6.93±4.95, $p=0.0116$).

Primary SS patients with FM had significantly higher tender point counts (8.89±6.45 *vs*. 2.43±4.87, $p<0.0001$) and widespread pain index (WPI) (8.54±3.65 *vs*. 3.12±2.16, $p<0.0001$) compared to those without FM. How-

ever, there was no significant difference in symptom severity scale (SS scale) between the both groups (7.74±3.65 *vs*. 6.81±4.53, p=0.1427). In bivariate correlation analyses, tender point counts were significantly correlated with WPI (Pearson correlation coefficient r=0.6432, p<0.0001) and SS scale (r=0.5429, p<0.0001) in pSS patients. Besides, tender point counts were significantly correlated with VAS of pain (r=0.6910, p<0.0001) or fatigue (r=0.6208, p<0.0001), ESSPRI (r=0.6123, p<0.0001), HAM-D scale (r=0.6313, p<0.0001), and CRP (r=0.3630, p=0.0012). Similarly, WPI and SS scale were significantly correlated with ESSPRI (r=0.6542 and r=0.7173, both p<0.0001) and HAM-D scale (r=0.6734 and r=0.6471, both p<0.0001) in pSS patients. However, tender point counts, WPI, and SS scale were not significantly correlated with ESSDAI.

When the severity of depression was classified by HAM-D scale, mild depression (HAM-D scale of 8-16) and moderate-to-severe depression (HAM-D scale ≥17) were founded in 36/100 (36.0%) and 21/100 (21.0%) pSS patients, respectively. The prevalence of FM in pSS with moderate-to-severe depression was significantly higher than that in pSS with mild depression or without depression (odds ratio=10.62, [95% confidence interval: 2.62-42.98], p=0.0009). HAM-D scale was significantly correlated with VAS of pain (r=0.6552, p<0.0001) and fatigue (r=0.7192, p<0.0001), ESSPRI (r=0.7179, p<0.0001), serum 25-(OH) Vit D3 levels (r=-0.4507, p=0.0003), and CRP (r=0.3122, p=0.0091) in pSS patients. Besides, HAM-D scale was positively correlated with FIQR score in pSS patients with concomitant FM (r=0.5341, p=0.0031). In multivariate linear regression analyses, HAM-D scale and ESSPRI were independently associated with increase in tender point count and SS scale (Table II).

The VAS of pain and fatigue, and ESSPRI in pSS with FM were significantly higher than those in pSS without FM. In addition, insomnia and cognitive dysfunction in pSS patients with FM were more common than those in pSS patient without FM. FM in pSS was not associated with the presence of autoantibodies, extra-glandular involvement, or its disease activity based on ESSDAI (Table III). Serum β2-microglobulin and total IgG levels in the two groups were comparable to each other. Serum 25-(OH) Vit D3 levels in pSS patients with FM were significantly decreased compared to those in pSS without FM (Table III). In particular, severe vitamin D deficiency with 25-(OH) Vit D3 ≤10 ng/mL in pSS patients with FM was more frequent than those in pSS without FM (35.5% (11/31) *vs*. 11.6% (8/69), p=0.0111). In pSS patients, serum 25-(OH) Vit D3 levels were negatively correlated with ESSPRI (r=-0.3926, p=0.0141) and ESSDAI (r=-0.3021, p=0.0221). In multivariate linear regression analyses, serum 25-(OH) Vit D3 levels independently contributed to the decrease of HAM-D scale (β=-0.41, p<0.0001; adjusted R^2=0.25).

Table II. Predictors of widespread pain index (WPI), symptom severity (SS) scale, and tender point count in primary Sjögren's syndrome*.

	WPI β (P)	SS scale β (P)	Tender point count β (P)
Age	0.03 (0.76)	- 0.14 (0.09)	- 0.09 (0.38)
Disease duration	0.01 (0.98)	0.07 (0.41)	0.12 (0.24)
Serum CRP level	- 0.03 (0.74)	0.04 (0.65)	0.18 (0.08)
Serum 25-(OH) Vit D3 level	0.04 (0.69)	0.09 (0.35)	0.12 (0.29)
ESSDAI	0.01 (0.99)	0.01 (0.89)	0.03 (0.82)
ESSPRI	0.63 (<0.001)	0.47 (<0.001)	0.29 (0.048)
Autoantibody (anti-SSA) positivity	- 0.05 (0.61)	- 0.10 (0.19)	- 0.01 (0.98)
Extra-glandular involvement	0.06 (0.03)	- 0.06 (0.51)	0.13 (0.22)
HAM-D scale	0.13 (0.35)	0.37 (.005)	0.39 (0.012)
The model fit (R^2)	0.564	0.653	0.507

*Results are from multivariate linear regression analyses. CRP: C-reactive protein; 25-(OH) Vit D3: 25-hydroxy vitamin D3; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; HAM-D: Hamilton-depression rating scale 17-items.

Table III. Difference of clinical manifestations between primary Sjögren's syndrome (pSS) patients with fibromyalgia (FM) and those without FM*.

	pSS with FM (n=31)	pSS without FM (n=69)	p-values
Age (years)	54.9 ± 9.1†	58.2 ± 11.6	0.4157
Disease duration (years)	9.6 ± 5.8	8.2 ± 6.7	0.3234
Menopause (%)	27 (87.1)	53 (76.8)	0.2889
History of thyroid disease (%)	7 (22.6)	18 (26.1)	0.8060
Extra-glandular involvement (%)	16 (51.6)	28 (40.6)	0.2845
Body mass index (kg/m^2)	22.4 ± 2.8	21.6 ± 2.9	0.2494
ESR (mm/h)	25.60 [12.00-40.75]‡	21.50 [12.5-55.50]	0.6628
CRP (mg/dL)	0.34 [0.01-0.98]	0.14 [0.01-0.30]	0.3782
Serum total IgG (mg/dL)	1675 [1507-1912]	1596 [1320-1921]	0.3864
Serum β2-microglobulin (mg/dL)	1.76 [1.16-2.41]	1.39 [1.19-1.94]	0.3301
Serum 25-(OH) Vit D3 (ng/mL)	12.45 [8.82-26.25]	24.30 [14.90 - 32.88]	0.0072
Anti-SSA/Ro antibody (%)	26 (83.9)	61 (88.4)	0.5343
Anti-SSB/La antibody (%)	23 (74.2)	42 (60.9)	0.2584
VAS of pain (0-100)	68.4 [41.7-95]	21.7 [5-57.4]	<0.0001
VAS of fatigue (0-100)	74.2 [53.4-94.2]	35.2 [5-61.2]	<0.0001
ESSPRI (0-10)	6.87 [6.06-8.38]	3.50 [1.50-6.19]	< 0.0001
ESSDAI (0-123)	3.0 [1.5-9.0]	2.0 [1.0-9.0]	0.2208
HAM-D scale (0-54)	17.5 [9.8-26.8]	6.0 [4.0-12.0]	< 0.0001
Insomnia, current (%)	26 (83.9)	18 (26.1)	< 0.0001
Cognitive dysfunction, current (%)	21 (67.7)	7 (10.1)	< 0.0001

*Classified according to the ACR 2010 criteria. ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; 25-(OH) Vit D3: 25-hydroxy vitamin D3; VAS: visual analogue scale; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; HAM-D: Hamilton-depression rating scale 17-items; † Mean ± SD; ‡ median with interquartile range.

Discussion

FM can be easily misdiagnosed as Sjögren's syndrome or vice versa as sic-

ca symptoms are well recognised in FM patients. In previous studies, the prevalence of FM in pSS patients has been reported to be diverse, ranging from 10 to 50%. However, the prevalence of FM is estimated at 2~7% in the general population (4, 14-18). Interestingly, the prevalence of FM in Sjögren's syndrome tends to be lower in recent studies (Table IV). Such results might be due to different criteria used for identifying Sjögren's syndrome since AECG criteria further require evidence of autoimmunity such as positive anti-SSA/Ro and/or anti-SSB/La or histologic finding of focal lymphocytic sialadenitis compared to previous classification or diagnostic criteria for Sjögren's syndrome (7). Thus, patients presenting with sicca symptoms suggestive of pSS who do not satisfy diagnostic criteria such as dry eye and mouth syndrome (19) could be part of spectrum of diseases related to FM. Since FM is not considered an autoimmune disorder, differential diagnosis or co-existence of FM should be evaluated for patients with sicca symptoms.

Dry eye and mouth, blurred vision, itching skin, fatigue, and insomnia can be somatic symptoms present in FM. However, these symptoms are also common features of Sjögren's syndrome. One study reported that pSS patients failed to show a decrease in fatigue in the first hour after awakening, unlike SLE and RA patients (20). Sleep disturbance which may result from nighttime sicca symptoms is often an overwhelming problem in pSS patients. It is associated with increased fatigue in the daytime (21). In the present study, there was no significant difference in SS scale between pSS patients with FM and those without FM. Furthermore, when FM was defined by the ACR 2010 criteria, the prevalence of FM in pSS tended to increase compared to FM classified by the ACR 1990 criteria. Although there was no significant difference in the severity of pain or fatigue or FIQR between FM patients who only met the ACR 2010 criteria and those who met the ACR 1990 criteria, SS scale in pSS patients with FM only meeting the ACR 2010 criteria was increased more. Since the ACR 2010 criteria consist of quantitative measures of body pain and the sum of the severity scale of fatigue, waking unrefreshed, and cognitive symptoms plus the extent of somatic symptoms in general, the diagnosis of FM according to the ACR 2010 criteria may be overestimated in Sjögren's syndrome.

Table IV. Summary of previous reports on prevalence of fibromyalgia (FM) in primary Sjögren's syndrome (pSS).

Investigator	Country (year)	Prevalence of FM* (%)	Number of pSS patients	Classification criteria of pSS
Vitali *et al*. (14)	Italy (1989)	47	30	Copenhagen 1986
Dohrenbusch *et al*. (15)	German (1996)	44	18	Copenhagen 1986
Tishler *et al*. (16)	Israel (1997)	55	65	Copenhagen 1986
Giles *et al*. (4)	England (2000)	12	75	European II 1996
Ostuni *et al*. (17)	Italy (2002)	22	100	European II 1996
Iannuccelli *et al*. (18)	Italy (2012)	18	50	AECG 2002 †
Current study	Korea (2014)	19 (31) ‡	100	AECG 2002

*FM classified according to the ACR 1990 criteria; †AECG: American-European Consensus Group; ‡FM defined by the ACR 2010 Criteria.

Previous studies have suggested that concomitant FM in autoimmune disorder may increase pain and physical limitation instead of contributing to autoimmune disease activity. For instance, it was reported that the presence of FM in SLE patients failed to predict more extensive organ involvement or lupus activity (22). However, since SLE patients with concomitant FM are highly symptomatic and dysfunctional, the clinical features of FM in these patients may contribute to a misinterpretation of lupus activity (23). Similarly, even disease activity score in 28 joint (DAS28) widely used in clinical practice and trials of RA may not be sufficient to evaluate the real inflammatory activity in RA patients with FM since tender joint counts and patient's general health are subjectively influenced measurements (24). In pSS, the patients with widespread pain were reportedly to form a benign subgroup, with a lower prevalence of anti-SSB and extra-glandular manifestations (25). Our study showed that pSS patients with FM did not differ significantly in disease activity of Sjögren's syndrome (ESSDAI), inflammatory markers such as ESR and CRP, or the presence of autoantibody. However, pSS patients with FM complained of moderate-to-severe depression, insomnia, and cognitive dysfunction more frequently than those without FM. Moreover, the presence of FM in pSS patients was associated with worsened ESSPRI, which were significantly correlated with tender point counts, WPI, and SS scale. Our results suggest that it is important for physicians to identify potential coexistence of FM when pSS patient has severe fatigue/pain and functional disability unrelated to disease activity.

It has been reported that pSS patients often have mood disorder compared to healthy controls (26). In the present study, depression was common in pSS patients. Majority of the pSS patients with depression were classified into the mild group. However, the severity of depression (HAM-D scale) in pSS patients independently contributed to the increase in tender point counts and SS scale. In addition, it was positively correlated with ESSPRI. The relationship between depression and FM is not fully understood yet. It was hypothesised that chronic pain causes depression, and vice versa. Chronic pain syndromes are considered as variants of depression (27). In our study, concomitant FM in pSS patients with moderate-to-severe depression was more frequent than those with mild depression or without depression, suggesting that negative mood might be exaggerated in co-existing FM condition. Although the causality between FM and depression remained unclear in our cross-sectional study, these findings emphasise that it is necessary to exclude co-existing FM in pSS patient who present moderate-to-severe depression.

In a recent Danish cohort study, prior hospital contact due to autoimmune disease increased the risk of subsequent

mood disorder diagnosis (28). The elevated risk of developing a mood disorder in autoimmune diseases could be explained by the presence of brain-reactive antibodies, altered serotoninergic homeostasis by pro-inflammatory cytokine, and up-regulated activity of the hypothalamic-pituitary-adrenal axis. It was recently reported that the expression of P2X7 receptor which modulates the release of the inflammatory cytokines interleukin (IL)-1β and IL-18 may contribute to anxiety and/or depression in pSS patients (29). In our study, serum 25-(OH) Vit D3 level was negatively correlated not only with ESSPRI and ESSDAI but also with the severity of depression in pSS patients. In addition, severe vitamin D deficiency in pSS patients with FM was more frequently observed than that in pSS patients without FM. As vitamin D may play an important role in the maintenance of B-cell homeostasis (30), it might be considered that vitamin D deficiency partly contributes to the pathogenesis of B cell-mediated autoimmune diseases such as pSS and SLE. Besides, a recent systematic review confirms that there is a strong association between vitamin D deficiency and depression (31). Our findings imply that low vitamin D concentration may be associated with the development of depression or FM in pSS. Further longitudinal exploration is required to confirm vitamin D deficiency as risk factor of concomitant FM in pSS.

In conclusion, the results of present study highlighted that comorbid FM should be identified in pSS patients who have complaints of exacerbated fatigue/pain or moderate-to-severe depression. Our study suggests that concomitant FM in pSS is not associated with disease activity. However, concomitant FM in pSS might contribute to functional disability.

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