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ORIGINAL ARTICLE

Sex-Related Differences in Symptoms and Psychosocial Outcomes in Patients With Fibromyalgia: A Prospective Questionnaire Study

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Abstract

Objective: To investigate sex-related differences in patients with fibromyalgia (FM) in terms of demographic characteristics and clinical features, including tender point count (TPC), mood disorders, sleep problems, FM symptom severity, fatigue, cognitive dysfunction, and quality of life (QOL).

Patients and Methods: We studied 668 consecutive patients with FM (606 women) from May 1, 2012, to November 30, 2013. Validated questionnaires assessed outcomes of depression (Patient Health Questionnaire-9), anxiety (Generalized Anxiety Disorder-7), sleep problems (Medical Outcomes Study Sleep Scale), FM symptom severity (Revised Fibromyalgia Impact Questionnaire), fatigue (Multidimensional Fatigue Inventory), cognitive dysfunction (Multiple Ability Self-report Questionnaire), and QOL (36-Item Short Form Health Survey). Nonparametric Mann-Whitney *U* and Pearson χ^2 tests were used to compare continuous and categorical outcome measures, respectively, between men and women. Linear regression models were performed for all continuous dependent variables, adjusting for age, body mass index, ethnicity, marital status, and highest education level completed. $P<.05$ was considered statistically significant. The Benjamini-Hochberg procedure was used to adjust for multiple comparisons.

Results: Multiple linear regression analysis revealed a significant association of female sex and greater TPC ($P<.001$), lower overall FM symptom severity (lower overall Revised Fibromyalgia Impact Questionnaire score; $P=.03$), and higher QOL subscale score for vitality (36-Item Short Form Health Survey vitality subscale score; $P=.02$). After adjustment for multiple comparisons, only the association between female sex and greater TPC remained significant. There were no sex-related differences in demographic characteristics, depression, anxiety, sleep problems, FM symptom severity, cognitive dysfunction, and QOL.

Conclusion: A higher TPC may be associated with female sex in patients with FM. The assumption of other sex-based differences in the clinical presentation of FM was not supported in our study.

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Fibromyalgia (FM) is a syndrome characterized by chronic widespread musculoskeletal pain that is typically also accompanied with fatigue, sleep disturbances, cognitive deficits, and psychiatric comorbid conditions.[1,2] Although the cause of FM is unclear, research suggests that neurochemical imbalances in the central nervous system may sensitize or amplify pain perception.[3-5] It is a prevalent disorder afflicting more than 5 million people in the United States.[6,7] Furthermore, FM has significant global impact and the prevalence is reported to be consistent among varying populations in different countries (2%-8% of the adult population).[8,9]

Fibromyalgia is considerably more common in women than in men, with women comprising about 85% to 95% of the total FM patient population across clinical studies.[10,11] Due to fewer men with the

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diagnosis, research in FM has primarily focused on women. Sex-related differences have been described in pain mechanisms,[12] health-related quality of life (QOL),[13] fatigue,[14,15] and psychiatric comorbid conditions[16] within the general population. However, limited studies have examined sex-based differences in the FM patient population, and findings to date are controversial and inconclusive.[17,18] Some studies report worse symptoms and clinical outcomes in men with FM,[19,20] some report worse outcomes in women with FM,[20,21] and some report no differences.[22-24] These discrepancies may be related to sociodemographic and geographical heterogeneity,[9,19,25] methodological flaws in observational studies not controlling for potential confounding factors,[24] and lack of use of validated instruments to evaluate outcome measures.[19]

Given the degree of variability in previous study findings, the objective of our prospective questionnaire study was to explore the association between sex and various clinical symptoms and psychosocial outcomes in the FM patient population. Similar to findings in the general population, we hypothesize that women with FM may experience worse clinical symptoms and psychosocial outcomes compared with men with FM. If sex-related differences are observed, findings from this study may be used to individually tailor diagnosis, treatment, and prognosis.

PATIENTS AND METHODS

Patient Population

This study was approved by the Institutional Review Board. All patients provided written consent to participate in the study. This was a prospective questionnaire study consisting of 668 total patients with FM who were referred to the Fibromyalgia and Chronic Fatigue Clinic at a tertiary referral center and completed the Fibromyalgia Treatment Program from May 1, 2012, through November 30, 2013.[17] All patients had a confirmed diagnosis of FM in accordance with the 1990 or 2010 American College of Rheumatology criteria.[2,26] The initial cohort consisted of consecutive patients who completed baseline questionnaires before attending treatment sessions at the program.

Outcome Assessment

Data for sex, demographic characteristics, and social variables were abstracted from the electronic medical record. Self-report questionnaires were used to assess tender point count (TPC), mood disorders (depression and anxiety), sleep disorders, fatigue, FM impact and symptom severity, cognitive dysfunction, and QOL.

The Patient Health Questionnaire-9 was used to assess depression.[27] Possible scores for each item ranged from 0 (not at all) to 3 (nearly every day). Scores of 5, 10, 15, and 20 represented thresholds for mild, moderate, moderately severe, and severe depression, respectively.[27] The Generalized Anxiety Disorder Scale is 7-item questionnaire used to assess anxiety, with each item scored from 0 to 3 and a total score ranging from 0 to 21.[28] Scores of 5, 10, and 15 represent mild, moderate, and severe levels of anxiety, respectively.

The Medical Outcomes Study Sleep Scale includes 6 dimensions of sleep and a 12-item measure for each dimension of sleep: disturbance, adequacy, quantity, somnolence, snoring, and shortness of breath. The Medical Outcomes Study Sleep Scale yields 2 summary scores: Sleep Problems Index I and Sleep Problems Index II. We used the Sleep Problems Index II (9 items) to assess sleep disorders. Summary scores range from 0 to 100, with higher index scores representing worse sleep.[29]

The Revised Fibromyalgia Impact Questionnaire (FIQ-R) is a 21-item self-report instrument that measures the functional status, symptom severity, and overall impact of FM.[29] All items are based on a scale of 0 to 10, with 10 indicating maximum impairment and 0 indicating no impairment. Weighted summary scores range from 0 to 100, with higher scores indicating more severe symptoms and scores of 0 to less than 39, 39 or higher to less than 59, and 59 or higher to 100 indicating mild, moderate, and severe symptoms, respectively.[30]

The Multidimensional Fatigue Inventory is a 20-item self-report instrument that measures the severity of fatigue.[31] It has 5 domains, including general fatigue, physical fatigue,

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reduced activity, reduced motivation, and mental fatigue. Each domain is scored from 4 to 20, with higher scores indicating greater fatigue. The Multidimensional Fatigue Inventory has been used in many clinical situations, including chronic fatigue syndrome[32] and FM,[33] and is considered a validated measure of fatigue.

The Multiple Ability Self-report Questionnaire was designed to measure self-perceived cognitive dysfunction, in contrast to traditional neuropsychologic measurements taken by clinicians.[34] It is a 38-item self-report measure that assesses 5 domains of perceived dysfunction: language ability, visual perception ability, verbal memory, visual spatial memory, and attention and concentration. Each item is scaled between 1 and 5, and scores on each cognitive domain range from 0 to 30 or 0 to 40. Each subscale is summed, with a maximum score of 190. Higher scores represent greater perceived cognitive difficulty.[29]

The 36-Item Short Form Health Survey (SF-36) is a validated questionnaire assessing health-related QOL. It has 8 subscales: physical functioning, role physical, body pain, general health, vitality, social functioning, role emotional, and mental health index. In addition, the SF-36 includes summary scores (physical component summary and mental component summary). The SF-36 total scores range from 0 to 100, with higher scores representing better health-related QOL measures.[35]

Statistical Analyses

Demographic and social characteristics were summarized using mean ± SD for continuous outcomes and frequency with percentage for categorical outcomes. Descriptive statistics were reported for all demographic and outcome measures. Nonparametric Mann-Whitney *U* and Pearson χ^2 tests were used to compare the continuous and categorical outcome measures, respectively, between men and women in our cohort. We also constructed linear regression models on all continuous dependent variables after adjusting for age, body mass index (BMI; calculated as the weight in kilograms divided by the height in meters squared), ethnicity, marital status, and highest education level completed. Because there were 30 separate statistical comparisons performed in this study, this raised the issue of multiple comparisons and concern for false-positive associations. Thus, although $P=.05$ is traditionally considered the threshold for statistical significance, we adjusted significance thresholds for each comparison by using the Benjamini-Hochberg false discovery control procedure with a set false discovery rate of 5%.[36,37] Data were analyzed using SPSS (IBM SPSS Statistics for Windows, version 21.0; IBM Corp). Given the observational nature of our study, causal inferences cannot be formulated.

RESULTS

This study included 668 patients (606 women) with a mean age of 47.2±13.0 years (range, 18-83 years). All demographic data are summarized in Table 1. There were no statistically significant differences in age, BMI, ethnicity, marital status, and education level completed.

Table 2 demonstrates all outcome measures based on sex. Unadjusted analysis using Mann-Whitney *U* test identified a correlation between female sex and greater TPC (14.9±3.7 vs 12.1±5.4; $P<.001$) and higher SF-36 subscale scores for vitality (16.4±13.9 vs 12.8±12.1; $P=.02$). These significant

TABLE 1. Demographic and Social Characteristics Based on Sex

Characteristic	Men (n=62)	Women (n=606)	*P*
Age (y), mean ± SD	48.3±12.2	47.1±13.1	.44
Body mass index (kg/m^2), mean ± SD	29.6±6.1	30.3±7.8	.71
White race, no. (%)	58 (93.5)	537 (88.6)	.24
Marital status, married, no. (%)[a]	49 (79.0)	437 (72.1)	.24
>12 y education completed, no. (%)	44 (71.0)	456 (75.2)	.09

[a]Married was defined as persons living with a partner in the same household regardless of legal marital status (this category excludes those who were divorced, widowed, separated, or single).

TABLE 2. Clinical Outcome Measures Based on Sex

Variable	Men		Women		Unadjusted *P*	Adjusted *P*
	No.	Score, mean ± SD	No.	Score, mean ± SD		
Tender point count	61	12.1±5.4	602	14.9±3.7	<.001[a]	<.001[a]
Generalized Anxiety Disorder-7						
Total	60	8.7±5.9	564	8.5±5.9	.73	.84
Patient Health Questionnaire-9						
Total	60	12.5±4.9	572	12.2±5.8	.54	.68
Sleep Problems Index II	60	57.7±15.1	596	58.1±19.2	.70	.98
Fibromyalgia Impact Questionnaire-Revised						
Function	60	13.3±6.7	591	15.1±7.4	.07	.15
Overall	61	13.8±4.6	597	12.4±5.6	.10	.03[b]
Symptoms	62	30.7±6.9	583	31.5±8.0	.19	.49
Total	60	57.3±14.8	573	59.0±18.4	.28	.70
Multidimensional Fatigue Inventory						
General fatigue	60	18.1±2.3	597	18.2±2.4	.58	.99
Physical fatigue	60	16.7±3.4	595	16.4±3.6	.61	.40
Mental fatigue	59	14.0±4.0	591	14.1±4.4	.65	.88
Reduced motivation	59	12.7±3.9	600	12.3±4.0	.61	.52
Reduced activity	60	15.8±3.7	599	14.9±4.3	.17	.10
Total	58	77.1±12.3	577	75.7±14.0	.67	.40
Multiple Ability Self-report Questionnaire						
Language ability	59	20.0±5.4	601	19.7±5.4	.98	.54
Visual perceptual	59	13.7±4.3	601	14.4±4.6	.17	.26
Verbal memory	60	23.2±5.4	601	22.1±5.9	.15	.11
Visual spatial	60	18.4±4.5	601	18.2±5.2	.60	.73
Attention	60	21.6±5.7	601	21.7±5.5	.80	.99
Total	60	96.3±22.6	601	96.1±22.8	.90	.82
36-Item Short Form Health Survey						
Physical functioning	61	29.5±17.6	593	31.2±20.9	.99	.42
Role physical	62	16.2±15.9	600	20.2±19.1	.09	.06
Body pain	62	13.7±13.9	600	16.4±16.4	.36	.15
General health	61	23.0±16.7	596	25.5±19.5	.44	.11
Vitality	62	12.8±12.1	602	16.4±13.9	.02[b]	.04[b]
Social functioning	62	18.9±25.2	591	22.8±25.9	.10	.16
Role emotional	60	29.5±31.8	597	36.2±31.8	.06	.09
Mental health index	61	34.3±26.1	600	38.8±25.4	.12	.16
Physical component summary	58	29.8±7.1	569	29.7±8.4	.85	.84
Mental component summary	58	36.9±12.5	569	38.4±12.4	.48	.39

[a]Statistically significant association after adjustment for multiple comparisons.
[b]*P* value was <.05 but did not achieve statistical significance after adjustment for multiple comparisons.

associations were also concordant with multiple linear regression analysis adjusting for covariates of age, BMI, ethnicity, marital status, and highest education level completed. In addition, adjusted analysis also revealed an association between female sex and lower overall FIQ-R score (12.4±5.6 vs 13.8±4.6; *P*=.03). There were no associations between sex and mood disorders (depression and anxiety), sleep problems, fatigue, cognitive dysfunction, and QOL. Although the association of female sex and higher vitality score and the association of female sex and lower overall FIQ-R score met the traditional statistical significance threshold of *P*<.05, these associations were no longer significant after

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adjustment for multiple comparisons using the Benjamini-Hochberg false discovery control procedure. Only the association between female sex and greater TPC remained statistically significant after adjustment for multiple comparisons.

DISCUSSION

Our study demonstrated that female sex may be a risk factor for greater TPC than male sex. This is consistent with several prior studies reporting that women with FM have significantly higher TPCs than men,[21,24,38] although some studies have also identified no significant differences.[19,39] Women have also been reported to feel pain more severely at these tender point sites.[19] A potential explanation for this association is the presence of a lower pain threshold in women.[40] Females generally exhibit higher sensitivity to noxious stimuli not only from mechanical pressure, but also from electric, thermal, ischemic, and cold stimuli.[21,41]

It is also plausible that complex biological factors from hormonal influences and psychosociocultural factors including sex expectations may play a role.[12,42] The manner in which palpation was performed when assessing for tender points may have varied between providers. Variations in skeletal, muscle, and fat body structures are other possible explanations.[21,43] Potential mechanisms through which sex hormones may affect pain sensation include its action on peripheral nociceptors,[44] central processing,[45] spinal inflammation,[46] and affective brain components that modulate pain perception.[47] Estradiol may be pronociceptive,[48] whereas studies have generally shown that testosterone and progesterone may play a protective role in pain severity.[49] Another theoretical mechanism is that serotonin is a neurotransmitter involved in the modulation of pain and is found is significantly higher proportions in males.[21,50] However, to date, the biochemical role of sex hormones and neurotransmitters in hyperalgesia of FM appears to be limited,[51] and these explanations remain speculative with no definitive evidence.

Historically, due to a heavy reliance on TPC as a determining factor of FM diagnosis per older diagnostic criteria, some authors claim that the greater frequency of women with FM diagnosed may be attributed to this criterion.[52] Therefore, in our study it is unclear whether TPC is associated with female sex in FM or if the overemphasis of the older diagnostic criteria on TPC may have diagnosed FM in more women than men. Revised diagnostic criteria in 2010 have eliminated TPC as a determining factor for FM diagnosis and as a result, recent systematic reviews have reported that sex-related differences in the prevalence are far smaller than previously thought,[11,53] and some have even reported sex ratios approaching equality.[54] Future studies should investigate whether the association of female sex and greater TPC remains significant if using solely the 2010 American College of Rheumatology Fibromyalgia Diagnostic Criteria for FM diagnosis.[2]

In our study, men and women had similar demographic characteristics in terms of race, marital status, and education level, consistent with prior studies.[19,21,24,35] Regarding mood disorders, the literature suggests that patients with FM have significantly more psychological symptoms than healthy controls.[55-57] In our study, the average total score on the Generalized Anxiety Disorder-7 (8.5±5.9) met criteria for mild to moderate anxiety, and the average total score on the Patient Health Questionnaire-9 (12.2±5.8) met criteria for moderate to moderately severe depression. Nevertheless, no sex-related differences were found in psychological symptoms between men and women with FM in our cohort. Our data are in agreement with other prior studies.[22,24,58]

Previous studies have demonstrated that men with FM may experience more severe limitations in physical and social functioning.[19,20,59] In our study, regression analysis also revealed an association between male sex and worse overall FM symptom severity as indicated by an increased overall FIQ-R score. However, after statistical adjustment for multiple comparisons, this association did not remain significant, which may be a component of an underpowered study. Furthermore, for domains of sleep problems, fatigue, QOL, and perceived cognitive dysfunction, our study did not demonstrate any sex-related differences. The literature is replete with inconsistency in regard to these outcome measures in

both the general population and FM population, and this may be partly attributed to different settings and use of variable and nonvalidated instruments.

Strengths present in our study included a prospective design, application of multiple linear regression analysis to adjust for confounders, and use of well-validated patient questionnaires to assess a broad spectrum of psychosocial outcomes. Although our study remains one of the largest observational studies in the literature investigating sex-related differences in the FM patient population, future larger-scale prospective trials, particularly with a larger sample size of men, are warranted. Cross-cultural trials using the same validated questionnaires would assess the impact of diverse backgrounds, health care systems, and cultural differences on sex and FM.[24] Furthermore, studies should investigate whether sex-related differences persist longitudinally over time and how individualized therapy and management can be implemented based on sex-related differences.

We identified several limitations in our study. Although our study included 668 consecutive patients and is one of the largest cohorts to date that seeks to determine sex-based differences among patients with FM, it may still not have been adequately powered to ascertain sex-related differences and increases the risk for type II statistical error. Importantly, we initially found significant associations between female sex and higher TPC, higher SF-36 subscale score for vitality, and lower overall FIQ-R score; however, after adjustment for multiple comparisons, only the association with TPC remained significant. Furthermore, it is difficult to determine a causal relation with our observational study. As mentioned, it is unclear whether TPC is associated with female sex in FM or whether the overemphasis of the older diagnostic criteria on TPC may have diagnosed FM in more women than men.

Another limitation was the lack of data for factors that may influence sex-related pain perception, including cultural differences and geographical region variation. Although our location took place in 1 hospital, it is a tertiary referral center that frequently cares for patients from across the United States and many other countries. Thus, it is plausible that regional factors from the patient's primary area of residence may affect their perception of pain, fatigue, and other psychosocial variables assessed in this study. Another limitation is that most of our patients (>70%) had completed more than 12 years of education, affecting the generalizability of our findings and thus its applicability to other health care institutions. Finally, reporting bias from self-report questionnaires is also a limitation.

CONCLUSION

The findings from this present study supported a significant association of higher TPC in female patients with FM compared with male patients with FM. Our data do not support consistent sex-specific differences in mood disorders, sleep problems, fatigue, FM impact and symptom severity, cognitive dysfunction, and QOL. Future studies with a larger male FM sample size are warranted.

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Abbreviations and Acronyms: **BMI** = body mass index; **FIQ-R** = Revised Fibromyalgia Impact Questionnaire; **FM** = fibromyalgia; **QOL** = quality of life; **SF-36** = 36-Item Short Form Health Survey; **TPC** = tender point count

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