

Fibromyalgia Is Common and Adversely Affects Pain and Fatigue Perception in North Indian Patients with Rheumatoid Arthritis

VARUN DHIR, ABLE LAWRENCE, AMITA AGGARWAL, and RAMNATH MISRA

ABSTRACT. *Objectives.* Fibromyalgia (FM) has been shown to be common in patients with rheumatoid arthritis (RA), but studies on Asian patients are lacking. It remains unclear whether FM has an adverse influence on pain, fatigue, quality of life, and mood in these patients, and what its relationship is with disease activity. We studied prevalence and effects of FM in North Indian patients with RA and associations of RA with disease activity.

Methods. This cross-sectional study included 200 RA patients and an equal number of controls. Presence of FM was defined using the American College of Rheumatology 1990 criteria. Pain and fatigue scores were assessed using a 10 cm visual analog scale. Quality of life and presence of depression/anxiety were determined using validated questionnaires. Disease activity and functional disability in RA patients was assessed using the Disease Activity Score 28-3 and Health Assessment Questionnaire, respectively.

Results. FM was present in 15% of patients with RA compared to 2.5% of controls in the North Indian population. RA patients with FM did not differ from those without FM in terms of age, gender, current disease-modifying agents, or steroid use. RA patients with FM had higher disease activity and worse functional disability. The number of tender and swollen joints was higher in patients with FM, but correlated poorly with each other. RA patients with FM had higher pain and fatigue scores but were not different in the quality of life or mood.

Conclusion. FM is more common in North Indian patients with RA compared to controls. It adversely affects the pain and fatigue felt by RA patients. Disease activity and FM influence each other. (First Release Oct 15 2009; J Rheumatol 2009;36:2443-8; doi:10.3899/jrheum.090157)

Key Indexing Terms:

RHEUMATOID ARTHRITIS
CHRONIC WIDESPREAD PAIN

FIBROMYALGIA

QUALITY OF LIFE
TENDER POINTS

Fibromyalgia (FM) is a syndrome characterized by widespread pain and the presence of tender points. The American College of Rheumatology (ACR) 1990 classification criteria for FM is the current standard for diagnosis¹. FM occurs in 1%–4% of the normal population, but has a much higher prevalence in rheumatic diseases like systemic lupus erythematosus (SLE), Sjögren's, and rheumatoid arthritis (RA)²⁻⁷. A possible explanation for its higher prevalence is central sensitization due to chronic inflammatory joint pain⁸. Indeed, in animal models deep nociceptive output can cause neuroplasticity and hyperexcitability in the nervous system, features found in FM⁹.

RA is a common rheumatic disease that affects 1% of the population.

In North America and Europe FM is more common in patients with RA than the general population, occurring in 8%–15% of these patients⁴⁻⁷. However, there are no data from Indian or Asian patients with RA. Therefore, we investigated the prevalence of FM in Indian patients with RA. In addition, we wanted to answer 2 questions: First, does FM have an adverse influence on pain, fatigue, mood, and overall quality of life in these patients? Second, what is the association of FM with disease activity? A recent study has found that assessment of disease activity using the Disease Activity Score (DAS28) is erroneous in RA patients with FM¹⁰.

MATERIALS AND METHODS

Data for our cross-sectional study were collected from January to November 2008. Informed written consent was obtained from all participating subjects, and the study was approved by the institutional ethics committee.

Subjects. Two hundred consecutive RA patients fulfilling the ACR 1987 criteria were recruited from the outpatient rheumatology clinic of a university hospital in North India. Patients with previously diagnosed renal failure or neuropathy were excluded. In all patients, disease activity and functional disability were measured using DAS28-3 (Disease Activity Score 28

From the Department of Clinical Immunology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India.

V. Dhir, MD, Senior Resident; A. Lawrence, DM, Assistant Professor; A. Aggarwal, DM, Additional Professor; R. Misra, MD, Professor, Department of Immunology.

Address correspondence to Dr. A. Lawrence, Department of Immunology, SGP GIMS, Lucknow 226014, India. E-mail: abledoc@gmail.com

Accepted for publication June 26, 2009.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2009. All rights reserved.

joints with 3 variables) and the Health Assessment Questionnaire-Disability Index (HAQ-DI), respectively^{11,12}. Two hundred healthy gender-matched controls from nursing staff working at the hospital were also included in the study.

Fibromyalgia assessment. The presence of FM was ascertained using the American College of Rheumatology (ACR) 1990 criteria for FM¹. Severity of FM or allodynia was assessed using a manual tender point survey¹³. Briefly, in addition to rating the 18 FM points as tender or not, subjects also rated the tenderness on a scale of 0–10. Three control points (center of forehead, left thumbnail, and right mid-forearm) were similarly scored. Individual point scores were averaged to obtain the FM and control intensity scores. All points were assessed by either of 2 examiners (VD or AL) using the dominant hand thumb pad with a force steadily increased to reach 4 kg pressure.

Fatigue, pain, and disturbed sleep. All subjects marked a 10 cm visual analog scale (with centimeter markings) for pain and fatigue felt in the preceding week. Subjects were asked whether they had difficulty in sleep (yes/no).

Quality of life. This was assessed using the World Health Organization quality of life BREF (WHO QoL BREF). We used the WHO QoL BREF UK English version and a validated Hindi version^{14,15}. This consists of 26 questions with 5 possible responses; final scores consist of mental, physical, psychological, and environmental domain scores (transformed to 0–100), a higher score reflecting better quality of life.

Depression and anxiety. Presence of anxiety and depression was determined using the English and Hindi versions of the Hospital Anxiety and Depression Scale¹⁶. This is a self-administered questionnaire consisting of 14 questions, 7 each for anxiety and depression. In addition, the Brief Patient Health Questionnaire and its Hindi version consisting of 9 questions were used for assessing depression¹⁷.

Data analysis. Statistical analysis was done using the SPSS software version 10.0 (SPSS, Inc., Chicago, IL, USA). Means of normally distributed continuous variables were compared using Student's *t* test, whereas Wilcoxon sign-rank test was used for nonparametric variables (number of tender points and tender point intensity). Categorical variables were compared by chi-square test. Correlation was performed using Pearson's coefficient of correlation. For multiple comparisons, Bonferroni correction was applied and the corrected *p* value was calculated.

RESULTS

Our study included 200 patients with RA and an equal number of controls. There was no difference between the groups in the gender ratio (female:male 5.7:1 vs 4.7:1; *p* = not significant, NS); however, patients were older (46.8 ± 10.7 vs 38.7 ± 8.8 yrs; *p* < 0.05) and less educated than controls (school completed 71.7% vs 97%; *p* < 0.05)

FM in RA patients and controls. FM was present in 30 patients with RA (15%) compared to 5 controls (2.5%). RA patients had a higher number of FM tender points (4.5 ± 5.3 , 0.7 ± 2.2 ; *p* < 0.001) and control tender points (0.2 ± 0.6 , 0.02 ± 0.3 ; *p* < 0.001) than controls. In addition, they had higher tender point intensity scores, both at the FM and control points (1.0 ± 1.4 vs 0.1 ± 0.5 , *p* < 0.01; 0.2 ± 0.7 vs 0, *p* < 0.01). The number of FM tender points as well as the tender point intensity score in RA patients correlated with the DAS28-3 and with the swollen joint count and erythrocyte sedimentation rate (ESR; Figure 1).

Characteristics of RA patients with and without FM. RA patients with FM were similar in age, gender, and current

treatment compared to those without FM, except for higher use of hydroxychloroquine and lower numbers finishing school (Table 1). They had higher disease activity, including higher tender and swollen joint counts, and worse functional disability (Table 1). However, patients without FM had good associations between tender and swollen joint counts (*r* = 0.64, *p* < 0.05), whereas patients with FM had no such association (*r* = 0.31, *p* = NS) and comparatively had more tender than swollen joints (Figure 2).

Effects of FM in patients with RA. RA patients with FM had more pain and greater fatigue, with a higher proportion having disturbed sleep (Table 2). On a linear regression model, both number of FM tender points and DAS28-3 were independent predictors of pain and fatigue in RA patients (combined *r* = 0.51, *p* < 0.001, and combined *r* = 0.50, *p* < 0.001, respectively). However, there was no significant difference in the prevalence of depression, anxiety, or quality of life among patients with RA with and without FM (Table 2).

DISCUSSION

We found the prevalence of FM in North Indian patients with RA to be 15% compared to 2.5% in controls. There are no studies on FM in RA from Asia; however, our results are similar to studies from other areas. Naranjo, *et al* found FM to be present in 14.8% of 386 Spanish patients with RA, while Wolfe, *et al* found a prevalence of 13.6% and 17.1% in 280 and 11,866 North American patients, respectively⁴⁻⁶. This similarity in results exists despite differences in the definition of FM. The current study and that by Naranjo, *et al* used the ACR 1990 criteria, whereas the earlier smaller study by Wolfe, *et al* required the presence of 7 tender points and skin-rolling tenderness⁴, whereas the recent larger study⁶ used survey criteria based on the regional pain score and fatigue score.

In contrast to our study in RA showing a similar prevalence of FM, an Indian study in SLE found a much lower prevalence of FM (8.2%)¹⁸ compared to studies in North America, Hong Kong, and Australia (17%–25%)^{2,19-23}. However, one North American study on a multiethnic SLE cohort showed a low prevalence of FM as well (5%)²⁴. The prevalence of FM in healthy nurses in our study is similar to Japanese hospital workers and general population surveys from Pakistan, the United States, and Europe²⁵⁻²⁸. There are no prior population surveys of FM in India. Interestingly, a systematic review from China found FM to be rare in the general population²⁹. There is a need for more population surveys in India and in the Asian population to further assess the role of ethnicity in this disease.

We found no difference in age, gender, or current treatment of RA patients with FM in our study. However, patients had higher disease activity and worse functional disability. The number of tender joints and swollen joints was increased, implying higher disease activity in RA patients with FM. This is at variance with a recent study that

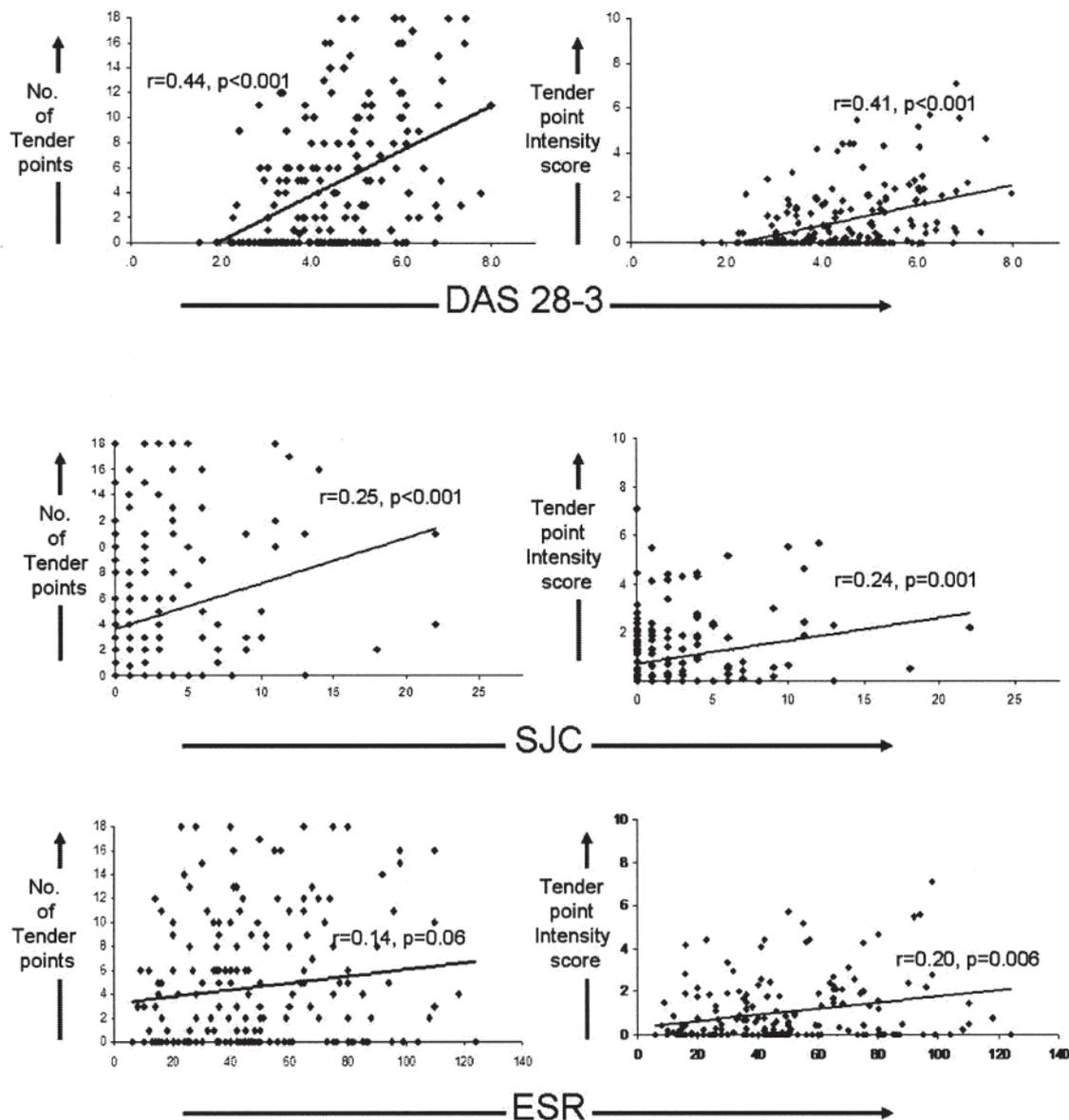


Figure 1. Comparison of FM tender point number and tender point intensity in relation to Disease Activity Score 28 joints with 3 variables (DAS28-3), swollen joint count, and erythrocyte sedimentation rate in patients with RA.

found only higher tender joint count and patient assessment in RA patients with FM. The investigators suggested the DAS28 was falsely elevated due to generalized tenderness¹⁰. As expected, we also found a disproportionate rise in tender joints compared to swollen joints in RA patients with FM (Figure 2). But, differing from that study¹⁰, we also found higher swollen joint counts and a correlation between FM tender points (and intensity score) with swollen joint counts and ESR (Figure 1). This suggests a more active disease is associated with FM in RA patients and may have a role in its development.

The presence of FM in RA was associated with higher pain and fatigue in our study. On a linear regression model, both were independently predicted by both number of tender

points and DAS28-3, suggesting an independent (of disease activity) effect due to FM. Wolfe, *et al* also found higher fatigue and pain scores in these patients⁴. Surprisingly, we did not find any additive worsening in the quality of life or mood due to the presence of FM in RA, although a negative impact is well established for both diseases separately^{30,31}. Also, Wolfe, *et al* had found worse mental and physical domains using the Medical Outcome Study Short Form-36 and poorer quality of life by Euro-Qol in RA patients with FM⁵. On a closer look at our data, patients with FM did indeed have poorer scores in most domains of quality of life and mood, although these were not statistically significant. The smaller number of patients (especially with FM) in our study may have led to a type 2 error.

Table 1. Characteristics of RA patients with and without fibromyalgia (FM).

Characteristic	Rheumatoid Arthritis		p (uncorrected)	p (corrected)
	With FM, n = 30	Without FM, n = 170		
Age, yrs, mean ± SD	46.3 ± 12.4	46.9 ± 10.3	NS	NS
Sex, female:male	9:1	4.7:1	NS	NS
School educated, %	62.3	73.5	0.006	NS
RA duration, yrs, mean ± SD	8.6 ± 6.6	8.6 ± 6.1	NS	NS
RF-positive, %	76.7	79.1	NS	NS
Methotrexate*, %	78.6	86.7	NS	NS
Sulfasalazine, %	14.3	7.3	NS	NS
Leflunomide, %	17.9	14.5	NS	NS
Hydroxychloroquine, %	53.6	33.3	0.050	NS
Steroids, %	53.3	45.2	NS	NS
Steroid dose, mg, mean ± SD	2.96	2.65	NS	NS
Current steroid taper**, %	24	14.8	NS	NS
TJC, 0–28, mean ± SD	11.4 ± 8.9	4.5 ± 5.7	< 0.001	< 0.05
SJC, 0–28, mean ± SD	4.3 ± 4.3	2.2 ± 3.6	0.002	< 0.05
DAS 28–3, mean ± SD	5.4 ± 1.2	4.3 ± 1.2	< 0.001	< 0.05
HAQ-DI, 0–3, mean ± SD	1.1 ± 0.7	0.7 ± 1.3	< 0.001	< 0.05
ESR mm/h, mean ± SD	54.5 ± 26	46.7 ± 25.3	NS	NS

* Current use of drug for all drugs listed. ** Reduction in dose or stoppage of steroids in the last 3 months. NS: not significant; TJC: tender joint count (28 joints); SJC: swollen joint count (28 joints); DAS 28–3: disease activity score (28 joints, 3 variables); ESR: Westergren erythrocyte sedimentation rate.

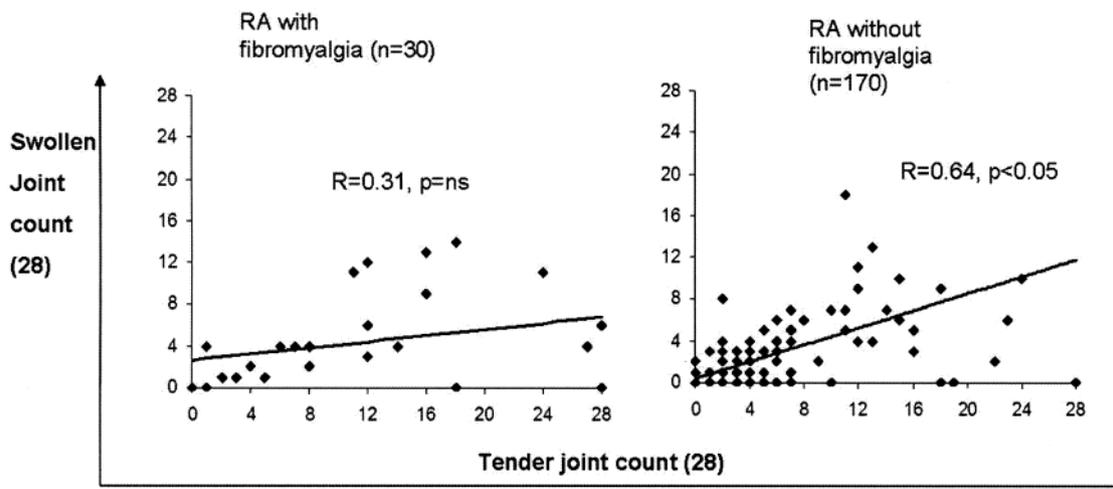


Figure 2. Swollen joint count (28 joints) in relation to tender joint count in patients with RA with FM (left panel) and without FM (right panel).

On the basis of our results, we speculate that a bidirectional relationship exists between FM and disease activity, with FM developing due to higher disease activity but subsequently leading to an erroneously higher estimation of tender joint count and hence disease activity. FM has an adverse effect on pain and fatigue in RA patients. We suggest that future interventional trials in RA should incorporate FM assessment to avoid erroneous overestimation of disease activity, as well as control for its effect on outcome. Further, a reassessment of FM in these patients after effective control of RA disease activity will lead to a

better understanding of its pathogenesis and significance in RA.

Among the strengths of our study are that it is the first from an Asian RA population. A major limitation is the lack of data on disease damage as a disease severity measure. Another drawback is the use of staff nurses as controls in our study, and not the general population.

To conclude, North Indian patients with RA have a higher prevalence of FM than healthy controls, and this is bidirectionally associated with disease activity. RA patients with FM had more pain and fatigue.

Table 2. Effect of fibromyalgia on patients with rheumatoid arthritis.

Characteristic	Rheumatoid Arthritis		p (uncorrected)	p (corrected)
	With FM, n = 30	Without FM, n = 170		
Pain VAS, 0–10, mean ± SD	5.4 ± 2.2	4.2 ± 2.3	0.013	NS
Fatigue VAS, 0–10, mean ± SD	3.9 ± 2.7	1.4 ± 2.3	< 0.001	< 0.01
Anxiety*, n (%)	8 (26.7)	42 (24.7)	NS	NS
Depression BPHQ**, n (%)	7 (23.3)	24 (14.1)	NS	NS
Depression HADS†, n (%)	6 (20)	29 (17.1)	NS	NS
Disturbed sleep, n (%)	16 (53.3)	49 (28.8)	0.018	NS
Physical score††, 0–100, mean ± SD	47.6 ± 11.4	51.9 ± 12.4	0.052	NS
Psychological score, 0–100, mean ± SD	52.0 ± 12.7	52.9 ± 15.4	NS	NS
Social score, 0–100, mean ± SD	66.5 ± 16.2	69.4 ± 20.5	NS	NS
Environmental score, 0–100, mean ± SD	59.6 ± 16.8	61.5 ± 18.0	NS	NS

*† Anxiety and depression assessed by Hospital Anxiety and Depression Scale. ** Depression assessed by Brief Patient Health Questionnaire. †† Domain scores of quality of life (WHO-QoL BREF). VAS: visual analog scale.

ACKNOWLEDGMENT

Acknowledgment of help in recruiting patients to our colleagues, Dr. B. Abujam, Dr. Y.P. Singh, Dr. S. Shukla, Dr. D.P. Shenoy, Dr. K. Bhatt, and Dr. R. Subramaniam. The material in this publication is the result of use of the WHOQOL-UK and the assistance of the University of Bath, and the World Health Organisation is acknowledged. Grateful acknowledgment is made of Dr. Puja Kocchar and Pfizer for permission to use the Brief Patient Health Questionnaire.

REFERENCES

- Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria committee. *Arthritis Rheum* 1990;33:160–72.
- Middleton GD, McFarlin JE, Lipsky PE. The prevalence and clinical impact of fibromyalgia in systemic lupus erythematosus. *Arthritis Rheum* 1994;37:1181–8.
- Vitali C, Tavoni A, Neri R, Castrogiovanni P, Pasero G, Bombardieri S. Fibromyalgia features in patients with primary Sjögren's syndrome. Evidence of a relationship with psychological depression. *Scand J Rheumatol* 1989;18:21–7.
- Wolfe F, Cathey MA, Kleinheksel SM. Fibrositis (fibromyalgia) in rheumatoid arthritis. *J Rheumatol* 1984;11:814–8.
- Wolfe F, Michaud K. Severe rheumatoid arthritis, worse outcomes, comorbid illness and socio-demographic disadvantage characterize RA patients with fibromyalgia. *J Rheumatol* 2004;31:695–700.
- Naranjo A, Ojeda S, Francisco F, Erausquin C, Rúa-Figueroa I, Rodríguez-Lozano C. Fibromyalgia in patients with rheumatoid arthritis is associated with higher scores of disability. *Ann Rheum Dis* 2002;61:660–1.
- Urrows S, Affleck G, Tennen H, Higgins P. Unique clinical and psychological correlates of fibromyalgia tender points and joint tenderness in rheumatoid arthritis. *Arthritis Rheum* 1994;37:1513–20.
- Martinez-Lavin M. Biology and therapy of fibromyalgia: Stress, the stress response system, and fibromyalgia. *Arthritis Res Ther* 2007;9:216.
- Wall PD, Woolf CJ. Muscle but not cutaneous C-afferent input produces prolonged increases in the excitability of the flexion reflex in the rat. *J Physiol* 1984;356:443–58.
- Coury F, Rossat A, Tebib A, Letroublon M, Gagnard A, Fantino B, et al. Rheumatoid arthritis and fibromyalgia: a frequent unrelated association complicating disease management. *J Rheumatol* 2009;36:58–62.
- Disease Activity Score in rheumatoid arthritis. [Internet. Accessed August 18, 2009.] Available from: <http://www.das-score.nl/www.das-score.nl/index.html>
- Fries JF, Spitz P, Kraines G, Holman H. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;23:137–45.
- Okifuji A, Turk DC, Sinclair JD, Starz TW, Marcus DA. A standardized manual tender point survey. I. Development and determination of a threshold point for the identification of positive tender points in fibromyalgia syndrome. *J Rheumatol* 1997;24:377–83.
- Skevington SM, Lotfy M, O'Connell KA; WHOQOL Group. The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. *Qual Life Res* 2004;13:299–310.
- Saxena S, Chandiramani K, Bhargava R. WHOQOL-Hindi: A questionnaire for assessing quality of life in health care settings in India. *World Health Organization Quality of Life. Natl Med J India* 1998;11:160–5.
- Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983;67:361–70.
- Kocchar PH, Rajadhyaksha SS, Suvarna VR. Translation and validation of Brief Patient Health Questionnaire against DSM IV as a tool to diagnose major depressive disorder in Indian patients. *J Postgrad Med* 2007;53:102–7.
- Handa R, Aggarwal P, Wali JP, Wig N, Dwivedi SN. Fibromyalgia in Indian patients with SLE. *Lupus* 1998;7:475–8.
- Gladman DD, Urowitz MB, Gough J, MacKinnon A. Fibromyalgia is a major contributor to quality of life in lupus. *J Rheumatol* 1997;24:2145–8.
- Akkasilpa S, Minor M, Goldman D, Magder LS, Petri M. Association of coping responses with fibromyalgia tender points in patients with systemic lupus erythematosus. *J Rheumatol* 2000;27:671–4.
- Wolfe F, Petri M, Alarcón GS, Goldman J, Chakravarty EF, Katz RS, et al. Fibromyalgia, systemic lupus erythematosus (SLE), and evaluation of SLE activity. *J Rheumatol* 2009;36:82–8.
- Tang S, Calkins H, Petri M. Neurally mediated hypotension in systemic lupus erythematosus patients with fibromyalgia. *Rheumatology* 2004;43:609–14.
- Morand EF, Miller MH, Whittingham S, Littlejohn GO. Fibromyalgia syndrome and disease activity in systemic lupus erythematosus. *Lupus* 1994;3:187–91.
- Friedman AW, Tewi MB, Ahn C, McGwin G Jr, Fessler BJ, Bastian

- HM, et al. Systemic lupus erythematosus in three ethnic groups: XV. Prevalence and correlates of fibromyalgia. *Lupus* 2003;12:274-9.
25. Toda K. The prevalence of fibromyalgia in Japanese workers. *Scand J Rheumatol* 2007;36:140-4.
26. Farooqi A, Gibson T. Prevalence of the major rheumatic disorders in the adult population of north Pakistan. *Br J Rheumatol* 1998;37:491-5.
27. Makela M, Heliövaara M. Prevalence of primary fibromyalgia in the Finnish population. *BMJ* 1991;303:216-9.
28. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum* 1995;38:19-28.
29. Zeng QY, Chen R, Darmawan J, Xiao ZY, Chen SB, Wigley R, et al. Rheumatic diseases in China. *Arthritis Res Ther* 2008;10:R17.
30. Martinez JE, Ferraz MB, Sato EI, Atra E. Fibromyalgia versus rheumatoid arthritis: a longitudinal comparison of the quality of life. *J Rheumatol* 1995;22:270-4.
31. Birtane M, Uzunca K, Tastekin N, Tuna H. The evaluation of quality of life in fibromyalgia syndrome: a comparison with rheumatoid arthritis by using SF-36 Health Survey. *Clin Rheumatol* 2007;26:679-84.