Fibromyalgia in patients with rheumatoid arthritis. A 10-year follow-up study, results from the Oslo Rheumatoid Arthritis Register

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ABSTRACT

Objective. *To examine cross-sectional and longitudinal relationships between fibromyalgia (FM) and rheumatoid arthritis (RA) disease activity.*

Methods. *636 patients in the observational Oslo RA register (ORAR) were invited to a clinical examination in 1999. 28-tender and swollen joint counts (TJC, SJC) and 18-tender points were assessed, the RA disease activity score (DAS-28) calculated. Fibromyalgia (FM) was diagnosed according to 1990 (FM-1990) and modified 2011 (mFM-2011) ACR criteria.*
At the 10-year follow-up patients completed the RA Disease Activity Index (RADAI) and Routine Assessment of Patient Index Data 3 (RAPID-3).
Baseline and 10-year RA disease activity were compared across presence/absence of FM. Linear regression models were constructed with 10-year RADAI and RAPID-3 as outcome.

Results. *502 patients participated at baseline data-collection and 10-year data was available in 236. At baseline, mean (SD) age was 59.5 (12.5) years and 87% were female. 9% and 30% had FM-1990 and mFM-2011 respectively. RA-FM patients were predominantly female with higher SJC, TJC, and DAS-28 at baseline. Baseline RA-FM predicted higher levels of RADAI and RAPID-3 at the 10-year follow-up.*

Conclusion. *RA-FM was associated with significantly higher levels of cross-sectional and longitudinal RA disease activity. FM should be considered in patients with RA not reaching remission.*

Introduction

Rheumatoid arthritis (RA) clinical disease activity is captured in composite scores which usually include swollen (SJC) and tender joint counts (TJC), in addition to patient and physician evaluations of global disease activity. Some instruments are entirely self-reported and convenient to use in large studies, such as Rheumatoid Arthritis Disease Activity Index (RADAI) and Routine Assessment of Patient Index Data (RAPID) (1). Low disease activity or sustained disease remission is the target of RA therapy.

Fibromyalgia is a disorder of pain perception characterised by widespread pain and fatigue. Lack of concentration, autonomic dysfunction and abdominal pain are additional symptoms. The 1990 classification criteria for FM (FM-1990) required presence of widespread pain in addition to pain in ≥11 of 18 tender points upon digital palpation (2). The 2010/2011 diagnostic criteria introduced the possibility of diagnosing FM (FM-2011) using a self-reported widespread pain index (WPI) and symptom scale (SS). The WPI is scored as the number of areas where the patient has experienced pain during the past week, graded 0 to 19. The SS is the sum of self-reported fatigue, cognitive symptoms, waking unrefreshed (each scored on a 0–3 scale), and presence of headache, abdominal pain and depression [present (1)/absent (0)] (3, 4). In the Fibromyalgia Symptom scale (FS) the sum of WPI and SS may function as a measure of FM disease activity (4), a cut-off of ≥13 has high sensitivity and specificity for the presence of FM diagnosed by clinical examination (4).

The estimated prevalence of co-existing FM in RA ranges from 6–49% (5-11). In cross-sectional studies presence of FM seems to be associated with higher RA disease activity (6, 9). It has recently been clarified that a diagnosis of FM according to the 2010/2011 diagnostic criteria may be made in patients with a concurrent rheumatic disease (12), but little is known of the relation between FM and RA disease activity in

Table I. Baseline cross-sectional associations in data assessment 1999.

Variable n (%)	Number with variable	FM-1990 n=40	No FM-1990 n=445	Adj. bivariate p	mFM-2011 n=152	No mFM-2011 n=350	Adj. bivariate p
Demographics							
Age, mean years (SD)	502	58.6 (12.2)	59.7 (12.5)	0.99	59.1 (11.7)	59.2 (12.9)	0.91
Female, n(%)	502	40 (100)	348 (78.2)	0.001	132 (86.8)	264 (75.4)	0.004
Current or past smoker, n(%)	494	22 (56.4)	284 (64.8)	0.47	95 (64.2)	223 (64.5)	0.83
Higher education, n(%)	472	8 (22.9)	147 (35.0)	0.10	39 (26.5)	123 (37.8)	0.02
BMI (kg/m^2), mean (SD)	473	22.8 (4.1)	24.5 (4.0)	0.04	24.5 (4.9)	24.2 (3.6)	0.25
RF positive, n(%)	431	16 (45.7)	202 (52.6)	0.47	64 (46.3)	159 (53.9)	0.15
Participated at 10-year follow-up	352	17 (54.8)	211 (68.3)	0.13	61 (58.1)	175 (70.9)	0.02
RA disease activity							
RA disease duration, mean years (SD)		16.3 (8.9)	14.9 (9.3)	0.54	17.3 (10.8)	14.1 (8.6)	0.001
ESR, mean (SD)	468	22.2 (23.0)	21.4 (18.3)	0.70	23.1 (20.0)	20.7 (18.1)	0.20
CRP, mean (SD))	475	17.4 (24.4)	14.5 (13.4)	0.14	16.5 (16.8)	14.0 (13.9)	0.06
DAS28, mean (SD)	449	5.3 (1.0)	4.4 (1.3)	<0.001	5.2 (1.2)	4.2 (1.3)	<0.001
Joint pain VAS, mean (SD)	495	44.8 (21.8)	34.9 (23.0)	0.02	52.8 (21.3)	27.9 (19.6)	<0.001
SJC, mean (SD)	499	9.8 (5.7)	6.8 (5.1)	0.001	8.4 (5.2)	6.4 (5.1)	<0.001
TJC, mean (SD)	496	13.3 (5.6)	7.4 (6.5)	<0.001	10.7 (6.6)	6.4 (6.2)	<0.001
Patient disease activity VAS, mean (SD)	485	46.7 (22.3)	37.1 (23.4)	0.02	55.0 (20.8)	29.9 (20.4)	<0.001
Fibromyalgia related variables							
Muscular tenderness VAS*, mean (SD)	471	59.1 (26.9)	32.0 (25.7)	< 0.001	65.3 (16.6)	18.6 (15.0)	<0.001
Fatigue VAS*, mean (SD)	494	65.7 (27.0)	42.8 (27.1)	< 0.001	64.3 (22.6)	35.7 (25.3)	<0.001
Headache VAS*, mean (SD)	430	19.9 (23.8)	14.4 (20.7)	0.24	27.1 (27.0)	9.1 (14.3)	<0.001
Abdominal pain VAS*, mean (SD)	474	37.1 (34.6)	19.1 (22.7)	< 0.001	35.2 (28.4)	13.9 (18.8)	<0.001
Concentration difficulty VAS*, mean (SD)	459	28.8 (27.1)	17.1 (19.5)	0.003	31.9 (24.2)	11.4 (14.4)	<0.001
Health Status							
HAQ, mean (SD)	444	1.37 (0.56)	1.10 (0.68)	0.06	1.5 (0.6)	0.9 (0.7)	<0.001
Co-morbidity score, mean (SD)	495	0.80 (0.99)	0.53 (0.76)	0.21	0.9 (1.0)	0.7 (1.0)	0.01

Unadjusted numbers presented. Level of significance was calculated using analysis of covariance (ANCOVA) models corrected for age and gender.
*The FM related variables at baseline were also corrected for baseline SJC 28 and CRP. FM-1990: fibromyalgia according to 1990 classification criteria; MFM-2011: fibromyalgia according to 2011 diagnostic criteria; BMI: body mass index; RF: rheumatoid factor; RA: rheumatoid arthritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS: disease activity score; VAS: visual analogue score; SJC: swollen joint counts; TJC: tender joint counts; HAQ: health assessment questionnaire.

Table II. Ten-year disease activity compared across baseline categories of fibromyalgia.

Variable n (%)	Number with variable	FM-1990 n=17	No FM-1990 n=211	Adj. bivariate p	mFM-2011 n=61	No mFM-2011 n=175	Adj. bivariate p
Demographics							
Age, mean (SD)	236	64.9 (10.1)	64.7 (11.4)	0.91	65.6 (10.6)	64.6 (11.6)	0.51
Female n (%)	236	17 (100)	175 (82.9)	0.60	55 (90.2)	139 (79.4)	0.06
RA disease activity							
Patient global*, mean (SD)	233	53.7 (21.7)	40.6 (23.7)	0.07	57.8 (17.9)	36.2 (22.9)	<0.001
RADAI*, mean (SD)	236	4.5 (1.4)	3.4 (1.6)	0.01	4.6 (1.4)	3.0 (1.5)	<0.001
RADAI inactivity*, n (%)	236	0 (0)	49 (23.2)	0.02	3 (4.9)	48 (27.4)	0.001
RAPID-3*, mean (SD)	206	5.3 (1.4)	4.2 (1.9)	0.06	5.4 (1.5)	3.9 (1.8)	<0.001
RAPID-3 remission*, n (%)	206	0 (0)	7 (3.8)	0.54	0 (0)	7 (4.8)	0.21
Fatigue VAS, mean (SD)[1]	233	62.8 (24.1)	48.1 (27.0)	0.13	67.0 (22.5)	43.3 (25.7)	0.002
Joint pain VAS, mean (SD)[2]	232	52.6 (20.7)	37.5 (24.3)	0.02	54.9 (19.6)	33.2 (23.4)	0.001
Health Status							
HAQ mean (SD)[3]	236	1.6 (0.3)	1.1 (0.7)	0.46	1.5 (0.6)	1.9 (0.7)	0.16

Unadjusted numbers presented. Level of significance was calculated using analysis of covariance (ANCOVA) models:
*Adjusted for age, gender, baseline CRP and baseline SJC.
[1]Adjusted for age, gender, baseline CRP, baseline SJC and baseline fatigue.
[2]Adjusted for age, gender, baseline CRP, baseline SJC and baseline pain.
[3]Adjusted for age, gender, baseline CRP, baseline SJC and baseline HAQ.
FM-1990; fibromyalgia according to 1990 classification criteria, MFM-2011; fibromyalgia according to 2011 diagnostic criteria, RA; rheumatoid arthritis, RADAI; RA Disease Activity Index, RAPID-3; Routine Assessment of Patient Index Data 3, VAS; visual analogue score, HAQ; health assessment questionnaire.

a longitudinal perspective. This paper examines the cross-sectional and longitudinal relationships between FM and clinical RA disease activity.

Patients and methods

Oslo RA register (ORAR) was established in 1994 as a prospective, observational, cohort study (13). The inclusion criteria were RA according to the 1987-ACR classification criteria, residency in Oslo and written consent. The study was approved by the Regional Committees for Medical and Health Research Ethics of South-Eastern Norway (281/98) and performed according to the Helsinki declaration.

Baseline examination

636 patients were asked to participate in a clinical examination in 1999. A trained study-nurse performed 28-TJC and 28-SJC and systematically assessed the 18-tender point count and calculated BMI (kg/m^2). Patients self-reported global disease activity and pain related to RA on a visual analogue scale (VAS), and completed the Stanford Health Assessment Questionnaire (HAQ) and Arthritis Impact Measurement Scales-2 (AIMS). Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and Rheumatoid factor (RF) were analysed consecutively. RA disease activity was calculated as DAS28 (ESR). Co-morbidities reported in AIMS were summed to create a co-morbidity score. FM-1990 was diagnosed when ≥11 tender points were reported (2). FM associated variables were registered in the 1999 data collection and this data was used to approximate the mFM-2011 criteria. For the SS scale; fatigue and concentration difficulties (scored 0-10 on a VAS) were divided into quartiles and scored as 0–3 in increasing order. The data-collection did not include a question concerning waking up unrefreshed. Presence of headache, abdominal pain (0-10 VAS) and AIMS depression were dichotomised at the third quartile (75%) and converted to 0 *vs*. 1. Muscular tenderness scored 0–100 on a VAS scale was converted into a 0–19 scale, and summed with the SS to give an approximation of the FS (4). Missing variables were imputed as 0. Patients with modified FS scale (mFS) ≥13 were given the mFM-2011 diagnosis (4).

Follow-up examination

At the 10th year of follow-up patients completed a questionnaire that included RADAI and RAPID 3.

Statistics

Baseline (1999) RA disease activity, health status and FM associated variables were compared across FM-1990 and mFM-2011. Level of significance was calculated using analysis of covariance (ANCOVA) models corrected for age and gender. The FM related variables at baseline were also corrected for baseline SJC 28 and CRP. RA disease activity at the 10-year follow-up was similarly compared across baseline fibromyalgia categories, corrected for baseline RA disease activity.

Longitudinal linear regression models were constructed with RADAI and RAPD-3 at the 10-year follow-up as the outcome in separate models. Variables of RA and FM disease activity were entered successively in univariate models that were adjusted for age and gender. Variables associated with the outcome (*p*≤0.1) were entered into a multivariate model, and subsequently removed by backwards selection. Separate models were constructed for FM-1990 and MFM-2011. Significance level in the models was set to *p*<0.05.

Results

502 (78.9%) patients were assessed at the baseline data-collection. The respondent rate (responding/invited) at the 10-year follow-up was 67% (236/352), 117 (23.3%) patients were deceased at the 10-year follow-up and 33 (6.6%) were lost to follow-up. Mean age (SD) at baseline was 59.5 (12.5) years, and 395 (78.9%) were female. The prevalence of FM-1990 was 8%, while 30% had mFM-2011. There were no significant differences in age, disease duration or participation at follow-up between patients who did and did not have FM-1990, but only women had FM-1990. Patients with mFM-2011 had longer disease duration and were less likely to participate at the follow-up (Table I). Details of missing data are presented in Table I. A comparison of participants *vs*. surviving non-participants at the 10-year follow-up is presented in Supplementary Table I.

At the baseline examination patients with RA-FM had higher DAS28, SJC, TJC, pain and patient global VAS, and borderline higher levels of CRP (Table 1) compared to patients without FM. FM-related symptoms such as muscular tenderness, fatigue, headache, abdominal pain and concentration difficulty were consistently more pronounced in patients with FM-1990 and mFM-2011 At the 10-year follow-up in 2009, patients with RA-FM had significantly higher levels of pain than patients without FM. Patients diagnosed according to mFM-2011 had also statistically significantly higher levels of fatigue and patient global VAS (Table II). A significantly lower number of RA-FM patients reached RADAI-inactivity compared to patients with only RA, and no patients with RA-FM reached RAPID-3 remission. In longitudinal linear regression models baseline tender-points and mFS-score were significant predictors of higher RADAI at the 10-year follow-up. The mFS-score also predicted higher RAPID-3 (Table III).

Discussion

In this study we report that patients with RA-FM are significantly less likely to achieve RA disease inactivity as defined by the RADAI instrument over at 10-year follow-up. Further, patients with secondary FM have higher levels of clinical RA disease activity, pain, and fatigue both in cross-sectional analyses and at the 10-year follow-up. FM was in this study diagnosed both according to the 1990 classification criteria and a modified 2011 diagnostic criteria and disease characteristics both regarding FM and RA were compared between the groups.

At the 10-year follow- up RA-FM was a negative predictor of RADAI inactivity. We have not found other studies that have investigated RA-FM as a longitudinal predictor of RA disease remission. Michelsen *et al*. however reported that discordance between patient's and physician's evaluation of RA disease activity, measured by TJC >SJC as well

Table III. Predictors RA disease activity at 10-year-follow-up in linear regression models.

	RADAI Adjusted for age and sex	RADAI Multivariate model 1	RADAI Multivariate model 2	RAPID3 Adjusted for age and sex	RAPID3 Multivariate model 1	RAPID3 Multivariate model 2
Demography						
Age (mean)	0.03 (0.02-0.03)**	0.03 (0.01-0.04)*	0.02 (0.00-0.04)*	0.04 (0.03-0.05)**	0.04 (0.01-0.06)*	0.04 (0.02-0.06)*
Female	0.31 (0.08-0.55)*	-0.49 (-0.93-0.13)	-0.44 (-0.97-0.09)	0.45 (0.13-0.76)*	-0.14 (-0.75-0.47)	-0.21 (-0.82-0.39)
Current or past smoker n(%)	0.31 (-0.12-0.75)			0.11 (-0.41-0.63)		
Higher education	-0.28 (-0.71-0.15)			-0.27 (-0.79-0.25)		
BMI (kg/m^2)	0.07 (0.01-0.13)*		0.06 (0.00-0.11)*	0.02 (-0.05-0.09)		
RF positive	-0.05 (-0.41-0.32)			0.27 (-0.17-0.71)		
RA disease activity						
RA disease duration	0.01 (-0.01-0.04)			0.03 (-0.01-0.06)¤		
DAS28 (mean)	0.36 (0.21-0.52)**			0.36 (0.21-0.52)**		
Pain (VAS 0-100)	0.03 (0.02-0.04)**	0.03 (0.02-0.04)**		0.04 (0.03-0.05)**	0.02 (0.01-0.03)*	
Fibromyalgia related variables						
Tender points	0.14 (0.08-0.19)**	0.09 (0.04-0.14)**	-	0.13 (0.07-0.20)**		-
mFS score	0.11 (0.08-0.14)**	-	0.09 (0.06-0.13)**	0.11 (0.07-0.14)**	-	0.08 (0.04-0.11)**
Health Status						
HAQ	0.92 (0.59-1.24)**		0.51 (0.17-0.85)*	1.35 (0.97-1.73)**	1.01 (0.58-1.43)**	1.05 (0.66-1.44)**
Comorbidity score	0.20 (-0.05-0.46)			0.20 (-0.05-0.46)		

Linear regression models. P: level of significance *$p<0.05$, **$p<0.001$.
Model 1: includes tender points; Model 2: includes FS score.
RA: rheumatoid arthritis; FM: fibromyalgia; BMI: body mass index; RF: rheumatoid factor; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS: disease activity score; VAS: visual analogue score; mFS score: modified Fibromyalgia Symptom Scale; HAQ: health assessment questionnaire.

as patient > physician VAS, reduced the likelihood of reaching disease remission (14). This is of relevance to our study as a difference of ≥ 7 between TJC and SJC has previously been launched as a surrogate of fibromyalgic RA (6).

In cross-sectional analyses we found that several parameters of clinical RA disease activity were significantly higher in patients with FM. This is in accordance with other studies (6, 10). In the ORAR the SJC was significantly higher in patients with RA-FM, while other studies are more heterogeneous regarding the relationship between SJC in RA and FM (6). An increase in patient global VAS or TJC could be a consequence of central sensitisation which is a key finding in FM, but an increased SJC suggests that FM could also be associated with higher levels of inflammatory RA disease activity (15).

In ORAR secondary FM-1990, was more prevalent than mFM-2011. A difference in prevalence between FM-1990 and mFM-2011 in patients with RA is also reported by others (6, 11), although we have to keep in mind that our data present an approximation of the FM-2011 questionnaire. Only women fulfilled the FM-1990 diagnostic criteria in this study, and a significantly higher proportion of women had mFM-2011, and this is in line with other reports (10). The distribution of FM-related symptoms was similar between patients with FM-1990 and mFM-2011, while RA disease duration seemed to be related to mFM-2011 but not FM-1990. The lack of clinical examinations at the 10-year follow-up is a weakness of the study, but validated self-reported instruments were employed. The study has several strengths; importantly the FM diagnosis was made by two separate criteria in a comprehensive longitudinal data-collection

Conclusion

RA-FM was associated with significantly higher levels of cross-sectional and longitudinal RA disease activity. RA-FM should be considered in patients with RA not reaching remission.

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