Elevated DAS28-ESR in patients with rheumatoid arthritis who have comorbid fibromyalgia is associated more with tender joint counts than with patient global assessment or swollen joint counts: implications for assessment of inflammatory activity

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Abstract

Objective

More than 20% of rheumatoid arthritis (RA) patients have comorbid fibromyalgia (FM+), which may elevate DAS28-ESR (disease activity score 28-erythrocyte sedimentation rate) and other indices, resulting in challenges to assess inflammatory disease activity. Although several reports indicate that elevated patient global assessment (PATGL) may elevate DAS28 in the absence of inflammatory activity, less information is available concerning the other three components, tender joint count (TJC), swollen joint count (SJC), and erythrocyte sedimentation rate (ESR), to possibly elevate DAS28 in FM+ vs. FM- RA patients.

Methods

A PubMed search identified 14 reports which presented comparisons of DAS28-ESR and its four components in RA FM+ vs. FM- groups. Median DAS28, component arithmetic differences, pooled effect sizes and 95% confidence intervals were analysed in the FM+ vs. FM- groups.

Results

In FM+ vs. FM- groups, median DAS28 was 5.3 vs. 4.2, SJC 4.0 vs. 3.0, TJC 13.2 vs. 5.3, PATGL 61.6 vs. 39.9, ESR 26.3 vs. 26.5. DAS28-ESR was classified as "high" (>5.1) in 11/14 FM+ groups and "moderate" (3.2-5.1) in all 14 FM- groups. Effect sizes in FM+ vs. FM- groups for DAS28-ESR, SJC, TJC, PATGL, and ESR were large (≥0.8) in 10/14, 1/13, 12/13, 7/13, and 1/13 comparisons, respectively, and pooled effect sizes 0.84 (0.3, 1.4), 0.33 (-0.4, 1.0), 1.27 (0.01, 2.5), 0.91 (-0.6, 2.4), and 0.07 (-0.6, 0.7), respectively.

Conclusion

DAS28-ESR is elevated significantly in FM+ vs. FM- RA patients; pooled effect sizes were highest for TJC, followed by PATGL, SJC and ESR. The findings appear relevant to response and remission criteria, treat-to-target, and general management of RA.

Key words

DAS28, fibromyalgia, rheumatoid arthritis, tender joint count, swollen joint count, patient global assessment

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Introduction

The DAS (disease activity score) (1) and DAS28 (2) to assess inflammatory activity in patients with rheumatoid arthritis (RA) include four measures, swollen joint count (SJC), tender joint count (TJC), patient global assessment (PATGL), and erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), derived from 7 RA core data set measures (3, 4). The formula to calculate DAS and DAS28, based on discriminant analyses and regressions, weights TJC at twice as much as SJC (1, 2). Treat-to-target directs escalation of therapy in routine care patients with moderate/ high scores for DAS28 or other indices such as the simplified disease activity index (SDAI) (5) and clinical disease activity index (CDAI) (5) toward low activity/remission, with possible exceptions in certain patients (6).

All measures included in the DAS28 and RA core data set are improved at statistically significant levels in patients randomised to active versus control treatments in randomized controlled clinical trials (RCTs) of biological agents and Jak inhibitors, facilitating introduction of many new agents over the last 2 decades (7). However, RCT protocols select for patients with high inflammatory activity and generally include only 5-30% of all RA patients (8, 9). In routine care, DAS28 and components may be elevated, independent of inflammatory activity, associated with comorbid depression (10-14), and fibromyalgia (FM) (15).

Recent attention to elevated DAS28 in the absence of substantial inflammatory activity has focused primarily on PATGL (16-19). RA Boolean remission criteria have been revised for maximum PATGL from 1 to 2 (19). However, less attention has been directed to the other 3 components in elevating DAS28 in RA patients with comorbidities such as FM.

These observations suggested that analyses of all 4 DAS28 components in RA patients who had comorbid FM (FM+) *vs*. no comorbid (FM-) might help clarify possible differences to elevate DAS28 as an indicator of inflammatory activity.

In this report, published comparisons of DAS28 and its 4 components, TJC, SJC, PATGL, and ESR or CRP, in FM+ and FM- RA patients were analysed for differences in the two patient groups. The primary goal of the report is not a comprehensive review, but to study relatively underrecognized differences between TJC (and PATGL) *vs*. SJC (and ESR) to elevate DAS28-ESR in patients with noninflammatory FM.

Methods

Data sources

A search was conducted in PubMed in 2021 using the terms "rheumatoid arthritis," "fibromyalgia," and "DAS28." Duplicates, abstracts, and non-English language reports were excluded. Inclusion criteria were: a) RA patients met American College of Rheumatology/ European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria (20) or earlier versions of RA Criteria; b) RA patients met criteria for FM, either 1990 (21), 2010 (22), 2011 (23) or 2016 criteria (24); c) mean or median of DAS28 and its four individual components, TJC28, SJC28, PATGL and ESR or CRP, were reported in FM+ and FM- RA patients. Reference lists of eligible studies were reviewed for additional relevant reports, but no further efforts were made to search other databases or to identify unpublished data (Fig. 1). As noted, the primary goal of this report is to call attention to differences between TJC and SJC to elevate DAS28-ESR in patients with FM, rather than to provide a comprehensive review.

DAS28 levels of disease activity are recognised as >5.1=high, 3.21–5.1=moderate 2.61–3.2=low, 0-2.6 = remission. FM 1990 criteria were based on the presence of ≥11 tender points on physical examination (21). Revised 2010 criteria included tender points, and patient self-report widespread pain index (WPI) and symptom severity scale (SSS) (22). Revised 2011 criteria included only the WPI and SSS self-report scores and did not include tender points (23). Revised 2016 criteria added a requirement for generalised pain in 4 of 5 regions of the body (24).

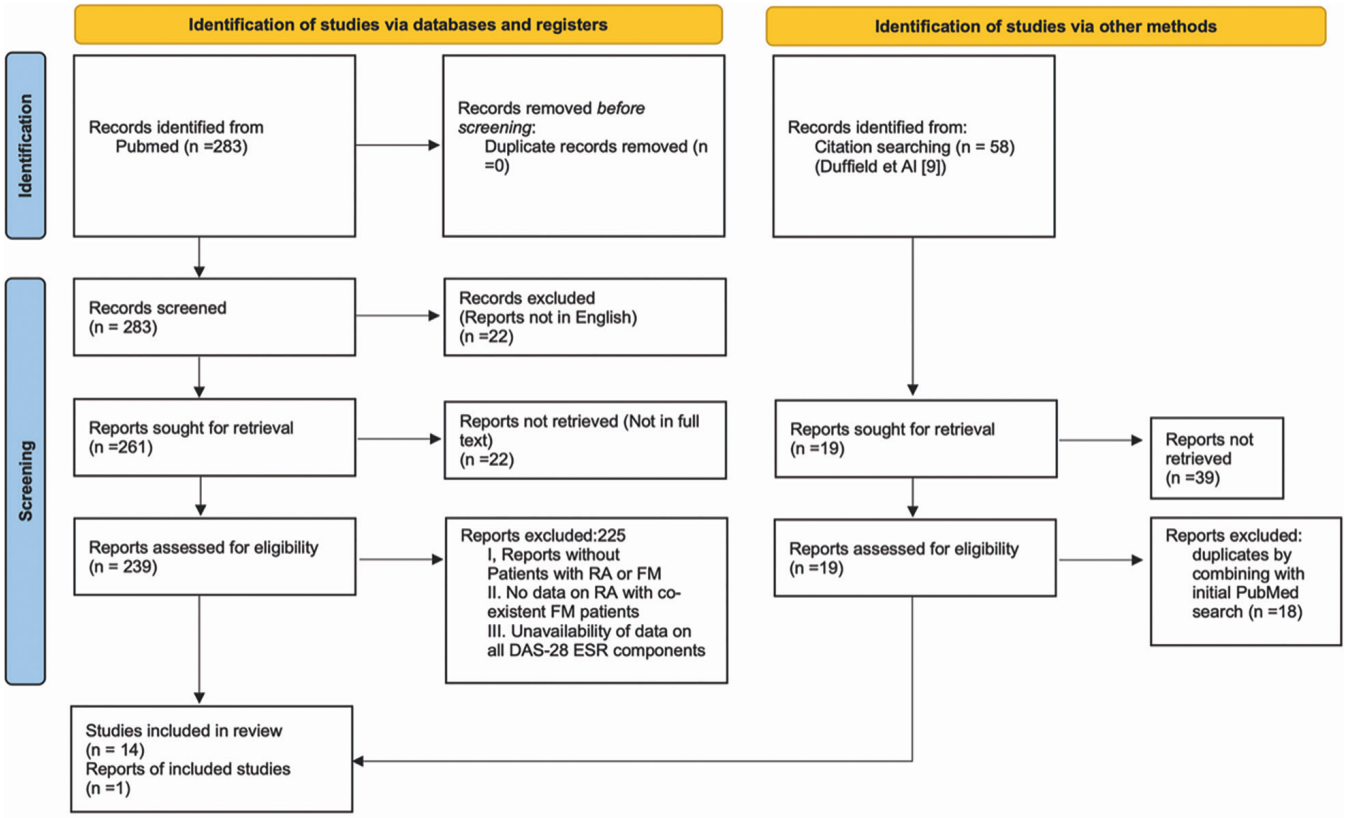

Fig. 1. PRISMA flow diagram (2020 updated algorithm for identification of studies from databases, registers and other methods).

Statistical analyses

FM+ and FM- RA groups were compared according to arithmetic differences, and effect sizes defined as the mean of FM+ minus the mean of FM- patients, divided by the standard deviation of FM- group. For studies in which mean values and 95% confidence intervals (CIs) were reported, the standard deviation of FM- was estimated under the assumption of a normal distribution. For studies in which medians and interquartile ranges (IQRs) were reported, means and standard deviations were estimated (25). Effect sizes were not calculated for studies that provided only means without standard deviations, either observed or estimated. Pooled effect sizes with corresponding 95% confidence intervals (CIs) were obtained by calculating mean effect sizes, with weights assigned based on the sample sizes of the studies, and correcting for sampling error across studies (26), Cohen has suggested that an absolute value of ≤0.2 is considered a 'small,' 0.21-0.79 'medium,' and ≥0.8 a 'large' effect size (27).

Patients in the FM+ *vs*. FM- groups were compared according to: four categories of DAS28-ESR activity, remission ≤2.8, low=2.81-3.2, moderate=3.2–5.1 and high>5.1; three categories of arithmetic differences, FM+ higher than FM-, FM+ equal to FM-, FM+ lower than FM-; and three categories of effect sizes, small ≤0.2, medium=0.21-0.79; and large ≥0.8.

Results

Literature search

The PubMed search results are summarised in Figure 1. The search identified 13 articles that met inclusion criteria, published between 2008 and 2019 (28-40). Two reports identified in the PubMed search are not included in our study, one which included only patients with early RA in ESPOIR cohort (41) and the other which reported patients with a median SJC of 0 in both FM+ and FM- groups, so effect sizes could not be calculated (42).

All included studies were cross-sectional studies of routine care patients who met ACR/EULAR criteria for RA (20) to compare DAS28 and its 4 components in patients who were FM+ or FM-. FM was ascertained by 1990 ACR criteria in 11 reports (28-35, 37, 38), by the revised 2010 criteria in one report (39), revised 2011 criteria in one report (36), and both the 1990 or 2011 FM criteria in one report (40) [no search results based the diagnosis of FM on 2016 criteria (24)]. The report which included both the 1990 and 2011 FM criteria (40) was incorporated into our review. Therefore, 14 comparisons of FM+ *vs*. FM- RA patients were available for analysis.

All included studies involved DAS28-ESR, and none DAS28-CRP. Seven reports involving 8 comparisons presented DAS-28-ESR components as means (28, 29, 32, 33, 35, 37, 40) and four as medians (31, 34, 36, 39). One report presented DAS28-ESR as a median and components as means (38). One report did not specify whether the values reported were means or medians and were presumed to be means (30).

DAS28-ESR in FM+ vs. FM- RA patients

DAS28-ESR was higher in FM+ *vs*. FM- RA groups all 14 comparisons

Table I. Mean or median DAS28-ESR in 14 comparisons of patients with rheumatoid arthritis (RA) who had comorbid FM fibromyalgia (FM+) or did not have comorbid fibromyalgia (FM-) and effect sizes of FM+/FM- groups.

STUDY*	Disease activity score-erythrocyte sedimentation rate (DAS28-ESR)[a]			
	Fibromyalgia positive	Fibromyalgia negative	Arithmetic difference	Effect size
¥ Vilaseca 2008[a] (28)	5.6 (0.78) H	3.4 (1.15) M	2.2	1.9
¥ Pollard 2010[c] (29)	6 (5.5, 6.5) H	4.3 (3.9, 4.6) M	1.7	1.0
¥ Toms 2010[d] (30)	5.4 (1.1) H	3.7 (1.4) M	1.7	1.2
¥ Kapoor 2011[b] (31)	4.8 (4.1, 5.3 M)	4.1 (3.2, 5.1) M	0.7	0.4
¥ Nawito 2013[a] (33)	5.6 (1.1) H	4.5 (1.3) M	1.1	0.8
¥ Zammurrad 2013[a,e] (32)	5.3 (1.5)[a] H	3.9 (1.2)[a] M	1.4	1.2
¥ Abbasi 2014[b] (34)	7.0 (6.6, 7.6 H)	4.9 (3.7, 5.7) M	2.1	1.5
¥ Ghib 2015[a, b] (35)	5.6 (0.7)[a] H	4.6 (1.1)[a] M	1.0	0.9
€ Joharatnam 2015[b, d] (36)	4.8 (4.4, 5.3)[b] M	4.4 (3.8, 4.9)[b] M	0.4	0.5
¥ Mian 2016[a] (37)	5.2 (0.8) H	4.1 (1.0) M	1.1	1.1
¥ Chakr 2017[a, b] (38)	5.3 (1.1)[a] H	3.9 (1.5)[a] M	1.4	0.9
Ø Salaffi 2018[b] (39)	4.5 (3.6, 4.7) M	3.8 (3.3, 4.3) M	0.7	0.7
¥ Provan 2019[a] (40)	5.3 (1.0) H	4.4 (1.3) M	0.9	0.7
€ Provan 2019[a] (40)	5.2 (1.2) H	4.2 (1.3) M	1.0	0.8
MEDIAN of (estimated) mean or effect size¶	5.3 H	4.2 M	1.1	0.9
Pooled effect size (95% CIs)				0.84 (0.33, 1.35)

¥ Diagnosis of FM by 1990 ACR Criteria; Ø: diagnosis of FM by modified 2010 Criteria; €: diagnosis of FM by modified 2011 Criteria; Provan *et al*. (40) included 1990 and 2011 criteria.
[a]Values reported as mean (standard deviation) unless otherwise indicated in the study;
[b]Values were reported as median (Interquartile range) unless otherwise indicated in the study;
[c]Mean (95% confidence interval);
[d]Study did not report the type of statistical measure used, presumed to be mean +/, SD or median with IQR;
[e]Mean without SD/95%CI/IQR.

Table II. Category of mean or median DAS28-ESR 14 studies of comorbid fibromyalgia (FM+) *vs*. no comorbid fibromyalgia (FM-) patients with RA according to the category of disease activity.

Index	Disease activity severity ≤2.8	Remission 2.81-3.2	Low 3.2-5.1	Moderate >5.1	High	Total # of studies
DAS28-ESR	Fibromyalgia positive	0	0	3 (21%)	11 (79%)	14 (100%)
	Fibromyalgia negative	0	0	14 (100%)	0	14 (100%)

(Table I). The median of mean or median DAS28-ESR in the FM+ RA patient groups was 5.3 (range 4.5-7.0), classified as high disease activity (>5.1), *vs*. 4.2 (range 3.4-4.9) in the FM- groups, classified as moderate disease activity (3.2-5.1) (Table I). Among the 14 comparisons, in the FM+ groups, 11 (79%) indicated DAS28–ESR high (>5.1) and 3 (21%) moderate (3.2–5.1) activity *vs*. moderate activity in all 14 FM- groups (Table II).

The median arithmetic difference of DAS28-ESR between the FM+ and FM- groups was 1.1 (range 0.4–2.2) (Table I). DAS28-ESR was higher in all 14 comparisons of FM+ *vs*. FM- groups (Table III). The pooled effect size was 0.84 (95% CIs: 0.33, 1.35), large and statistically significant (Table I). Effect sizes for FM+ *vs*. FM- groups were "medium" (0.2-0.79) in 4 comparisons (29%) and "large" (≥0.8) in 10 comparisons (71%) (Table III).

Comparisons of the 4 individual component measures, TJC, SJC, PATGL, and ESR to DAS28-ESR in FM+ vs. FM- RA patients

The median of mean or median SJC in the FM+ groups was 4.0 (range 1.1-9.8) vs 3.0 (range 0.8-6.8) in the FM- groups. The median difference was 0.7 and median effect size 0.1 (small) (Table IV). The pooled effect size for SJC was 0.33 with 95% CIs (-0.37, 1.02), in the lower range of medium and not statistically significant (Table IV).

The median of the mean or median of TJC in FM+ groups was 13.2 (range 8-24) *vs*. 5.3 (range 2.3-7.4) in the FM- groups. The median difference was 8.1 and median effect size 1.5 (large). The pooled effect size for TJC was 1.27 with 95% CIs (0.01, 2.53), large and statistically significant (Table IV).

The median of mean or median PATGL in FM+ was 61.6 (range 46.7-80) vs. 39.9(range 20-70) in FM- groups. The median difference was 23.1 and median effect size 0.9 (large) The pooled effect size for PATGL was 0.91 with 95% CIs (-0.58, 2.39), large but not statistically significant (Table V).

The median of mean or median of ESR in FM+ groups was 26.3 (range 19-39) *vs*. 26.5 (range 17-41.8) in the FM- groups. The median difference was 1.7 and median effect size 0.04 (small). The pooled effect size for ESR was 0.07 with 95% CIs (-0.58, 0.72), small and not statistically significant (Table V).

The data indicate moderate control of inflammatory activity with a median SJC of 4.0 in the FM+ groups versus 3.0 in the FM- groups (Table IV). By contrast, the median TJC was 13.2 in the FM+ groups *vs*. 5.3 in the FM- groups, a difference of 8.1 tender joints for TJC vs fewer than 1 joint for SJC (Table IV). Furthermore, 12/13 effect sizes were "large" for TJC *vs*. 1/13 for SJC, 7/13 for PATGL, and 1/13 for ESR (Table III).

Discussion

The results confirm previous observations that DAS28 is significantly higher in FM+ *vs*. FM- RA patients (15), and extend the findings with evidence that elevated DAS28 is explained primarily by TJC followed by PATGL. Furthermore, substantial differences are seen between TJC and SJC in elevating DAS28-ESR in the FM+ *vs*. FM- groups, with a median difference of 8.1 tender joints *vs*. less than 1 swollen joint in FM+ *vs*. FM- groups, respectively. The data indicate moderate control of inflammatory activity in both groups according to SJC with median levels of 4.0 in FM+ *vs*. 3.0 in

Table III. Number of 14 comparisons of RA patients with comorbid fibromyalgia (FM+) *vs*. no comorbid fibromyalgia (FM-) according to arithmetic differences and effect sizes of means or medians in the FM+ *vs*. FM- groups.

Category	DAS28-ESR	Swollen joint count (SJC)	Tender joint count (TJC)	Patient global assessment (PATGL)	Erythrocyte sedimentation rate (ESR)
FM+ higher than FM-	14 (100%)	8 (57%)	14 (100%)	14 (100%)	10 (71%)
FM+ equal to FM-	0	2 (14%)	0	0	0
FM+ lower than FM-	0	4 (29%)	0	0	4 (29%)
Small effect size ≤0.2	0	5 (38%)	0	1 (8%)	7 (54%)
Medium effect size 0.21-0.79	4 (29%)	7 (54%)	1 (8%)	5 (38%)	5 (38%)
Large effect size ≥0.8	10 (71%)	1 (8%)	12 (92%)	7 (54%)	1 (8%)
Total comparisons*	14 (100%)	13 (100%)	13 (100%)	13 (100%)	13 (100%)

*Effect size could not be calculated for DAS2-ESR components in one of the reports.

Table IV. Mean or median DAS28-ESR components, tender joint count (TJC) and swollen joint count (SJC) in patients with rheumatoid arthritis (RA) who had comorbid FM fibromyalgia (FM+) or did not have comorbid fibromyalgia (FM-) and arithmetic differences and effect sizes of FM+ *vs*. FM- groups.

STUDY*	Swollen joint count (0-28)				Tender joint count (0-28)			
	FM positive	FM negative	Difference	Effect size	FM positive	FM negative	Difference	Effect size
¥Vilaseca 2008[a] (28)	1.1 (1.4)	0.8 (1.8)	0.3	0.2	17.4 (9.5)	2.3 (5.1)	15.1	3.0
¥Pollard 2010[c] (29)	4 (2, 6)	4 (3, 4)	0	0	17 (14, 21)	6 (4, 7)	11	1.5
¥Toms 2010[d] (30)	4.9 (3.9)	3.0 (4.3)	1.9	0.5	14.1 (7.6)	2.9 (3.6)	11.2	3.1
¥Kapoor 2011[b] (31)	4 (1, 6)	3 (1, 6)	1.0	0.1	8 (6, 13)	4 (1, 8)	4	0.9
¥Nawito 2013[a] (33)	2.8 (3.2)	3 (4.1)	-0.2	-0.05	12.3 (9.1)	4.5 (4.2)	7.8	1.9
¥Zammurrad 2013[a,e] (32)	2.8[e]	1.7[e]	1.1		13.1[e]	4.1[e]	9	
¥Abbasi 2014[b] (34)	9 (2, 18)	3 (1, 7)	6	1.3	24 (24, 28)	5 (2, 12.5)	19	2.4
¥Ghib 2015[a, b] (35)	5 (0.7, 8)[b]	6 (0.7, 7.5)[b]	-1.0	-0.03	15 (11.7, 20.7)[b]	5.5 (2, 10)[b]	9.5	1.7
€ Joharatnam 2015 [b, d] (36)	1 (0, 2)[d]	1 (1, 2)[d]	0	-0.4	11 (7, 18)[d]	6 (4, 9)[d]	5	1.4
¥Mian 2016 [a] (37)	1.8 (2.3)	2.8 (3.5)	-1.0	-0.3	15.7 (5.8)	7.4 (5.4)	8.3	1.5
¥Chakr 2017 [a, b] (38)	3.9 (1, 5.5)[b]	2.4 (0, 5)[b]	1.5	0.3	10 (5, 17)[b]	3 (0, 8)[b]	7	1.2
ØSalaffi 2018[b] (39)	3 (1, 5.75)	4 (2, 6)	-1.0	-0.3	12 (7.3, 14)	6 (3, 8)	6	1.5
¥Provan 2019 [a] (40)	9.8 (5.7)	6.8 (5.1)	3.0	0.6	13.3 (5.6)	7.4 (6.5)	5.9	0.9
€Provan 2019 [a] (40)	8.4 (5.2)	6.4 (5.1)	2.0	0.5	10.7 (6.6)	6.4 (6.2)	4.3	0.7
MEDIAN ¶	4.0	3.0	0.7	0.1	13.2	5.3	8.1	1.5
Pooled effect size (95% CIs)				0.33 (-0.37, 1.02)				1.27 (0.01, 2.53)

¥: diagnosis of FM by 1990 ACR Criteria; Ø: diagnosis of FM by modified 2010 Criteria; €: diagnosis of FM by modified 2011 Criteria; Provan *et al*. (40) included 1990 and 2011 criteria.

[a]Values reported as mean (standard deviation) unless otherwise indicated in the study;

[b]Values were reported as median (interquartile range) unless otherwise indicated in the study;

[c]mean (95% confidence interval);

[d]Study did not report the type of statistical measure used, presumed to be mean +/, SD or median with IQR;

[e]Mean without SD/95%CI/IQR.

FM- patients. However, the median of 13.2 *vs*. 5.3, with a median difference of 8.1 tender joints, differences over more than 25% of the entire range of TJC, suggest that differences in TJC according to a non-inflammatory comorbidity of positive FM screening are considerably greater than differences in SJC. TJC appears more limited than SJC to assess inflammatory activity.

Large effect sizes in FM+ *vs*. FM- patients were seen in one of 13 comparisons for SJC, compared to 12/13 for TJC, 7/13 for PATGL, and 1/13 for ESR (Table III). Although explanation of elevated DAS28–ESR by elevated PATGL may have been anticipated based on published reports (16-19), TJC appears more explanatory than PATGL of elevated DAS28 in FM+ *vs*. FM- patients. Furthermore, the data indicate that SJC and ESR are far less likely to differ in FM+ *vs*. FM- patients than TJC and PATGL, and therefore may be regarded as more accurate indicators of inflammatory activity.

Elevations of DAS28 based on elevated TJC (and/or PATGL) have relevant implications for response and remission criteria, treat-to-target, and routine care. A TJC of 13/28 and PATGL of 63/100, the median values for FM+ RA patients (Table I), would result in DAS28-ESR of 4.51, indicating moderate activity (https://www.4s-dawn.com/DAS28), even if SJC were 0 and ESR 10 mm/hr. A TJC of 8 and PATGL of 46, the lower interquartile range of FM+ RA patients (Table I), would result in DAS28 of 3.84, again indicating moderate activity, if SJC were 0 and ESR 10 mm/hr. Therefore, assuming

Table V. Mean or median DAS28-ESR components, patient global assessment (PATGL) and erythrocyte sedimentation rate (ESR, in mm/h) in 14 comparisons of patients with rheumatoid arthritis (RA) who had comorbid FM fibromyalgia (FM+) or did not have comorbid fibromyalgia (FM-) and arithmetic differences and effect sizes of FM+ *vs*. FM- groups.

STUDY*	Patient global assessment				Erythrocyte sedimentation rate (ESR)			
	FM positive	FM negative	Difference	Effect size	FM positive	FM negative	Difference	Effect size
[¥]Vilaseca 2008[a] (28)	56.2 (21.0)	39.7 (26.6)	16.5	0.6	30.8 (17.3)	28.1 (16.1)	2.7	0.2
[¥]Pollard 2010[c] (29)	66 (55, 77)	40 (34, 46)	26	0.9	39 (22, 55)	27 (23, 32)	12	0.6
[¥]Toms 2010[d] (30)	60.4 (15.9)	32.6 (21.6)	27.8	1.3	28.5 (29.2)	39.4 (23.5)	-10.9	-0.5
[¥]Kapoor 2011[b] (31)	47 (33, 56)	40 (21, 59)	7	0.2	23 15, 54)	18 (10, 32)	5.0	0.7
[¥]Nawito 2013[a] (33)	64 (23.6)	46.8 (25.9)	17.2	0.7	38.2 (16.8)	41.8 (22.5)	-3.6	-0.2
[¥]Zammurrad 2013[a,e](32)	62.7[e]	38[e]	24.7		38.9[e]	31[e]	7.9	
[¥]Abbasi 2014[b] (34)	80 (70, 80)	20 (10, 30)	60	3.8	37 (26, 48)	40 (22, 60)	-3.0	-0.13
[¥]Ghib 2015[a, b] (35)	66 (15)[a]	44.5 (21)[a]	21.5	1.0	23 (7.2, 42.5)[b]	22 (13.7, 40)[b]	1.0	-0.05
[€]Joharatnam 2015[b, d] (36)	70 (55, 78)[d]	42 (24, 55)[d]	28	1.1	19 (8, 29)[d]	17 (12, 26)[d]	2.0	0.03
[¥]Mian 2016[a] (37)	57.1 (18.3)	49.5 (20.5)	7.6	0.4	20.5 (14.4)	19.2 (17.8)	1.3	0.1
[¥]Chakr 2017[a, b] (38)	56.5 (41.5, 90)[b]	31.5 (14, 52.2)[b]	25	1.1	28.5 (15.5, 49)[b]	26 (14, 41.2)[b]	2.5	0.2
[Ø]Salaffi 2018[b] (39)	80 (62.5, 90)	70 (60, 80)	10	0.5	24 (11.3, 34)	32 (22, 44)	-8.0	-0.6
[¥]Provan 2019[a] (40)	46.7 (22.3)	37.1 (23.4)	9.6	0.4	22.2 (23)	21.4 (18.3)	0.8	0.04
[€]Provan 2019[a] (40)	55.0 (20.8)	29.9 (20.4)	25.1	1.2	23.1 (20.0)	20.7 (18.1)	2.4	0.1
MEDIAN[¶]	61.6	39.9 2	2.7	0.9	26.3	26.5	1.7	0.04
Pooled effect size (95% CIs)				0.91 (-0.58, 2.39)				0.07 (-0.58, 0.72)

[¥]: Diagnosis of FM by 1990 ACR Criteria; [Ø]= Diagnosis of FM by modified 2010 Criteria; [€]= Diagnosis of FM by modified 2011 Criteria; Provan *et al*. (40) included 1990 and 2011 criteria.
[a]Values reported as mean (standard deviation) unless otherwise indicated in the study;
[b]Values were reported as median (interquartile range) unless otherwise indicated in the study;
[c]Mean (95% confidence interval);
[d]Study did not report the type of statistical measure used, presumed to be mean +/, SD or median with IQR;
[e]Mean without SD/95%CI/IQR.

a conservative prevalence of FM+ RA of 20% (15, 43), of whom 75% would have DAS28-ESR of at least 3.84, 15% of all RA patients would be classified as in moderate activity even if all had ESR SJC of 0 and ESR of 10 (https://www.4s-dawn.com/DAS28).

DAS28 and other RA indices also may be elevated significantly by comorbidities beyond fibromyalgia, independent of inflammatory activity (44), including comorbid depression, estimated to be seen in 9.5% - 41.5% of people with RA (10-14) and comorbid hand osteoarthritis (OA), seen in 52% of RA patients (45). Possible elevations of TJC and/or PATGL leading to an elevated DAS28 in the presence of considerable, little, or no inflammatory activity indicates a need for rheumatologists to actively interpret these scores.

This phenomenon is conceptually not different from a need to interpret an elevated ESR in an RA patient, in whom obesity, infection and/or neoplasm must be excluded before concluding the results are explained by RA inflammatory activity. One difference in these two phenomena may involve relatively established protocols to search for infection or neoplasm, while FM, depression, and joint damage usually are not recorded formally in routine rheumatology care (or in most RA clinical research including clinical trials). FM and depression appear underrecognized without formal patient self-report questionnaires (13, 23).

Recent attention to elevated DAS28 in the absence of substantial inflammatory activity has focused primarily on PATGL and not the other 3 DAS28 components activity (16-19). As a consequence, RA Boolean remission criteria have recently been revised for maximum PATGL from 1 to 2 (19). A proposed "dual target strategy" designed to "mitigate the risk of overtreatment" in RA (46) does not consider TJC, which may raise DAS28 and other RA indices as much as or more than PATGL, as documented in this report. Furthermore, ACR/EULAR ACR20, 50, and 70 response criteria require 20%, 50%, and 70% improvement in TJC (and SJC), regardless of any other changes in core dataset measures(47). RA patients with FM are less likely show improvement in TJC and therefore be ineligible for even modest ACR 20 responses, which may explain in part why almost all clinical trials other than in patients selected for early disease do not indicate an ACR 20 response in more than 60-70% of patients (48).

It may further appear disappointing that all FM- groups were in "moderate" DAS28 activity, and no group in "low" activity or remission despite more than a decade of treat-to-target (6). The included studies were reported between 2008 and 2019, possibly reflecting earlier results before widespread use of biological agents to treat RA. In addition, some of the reports were from countries with low gross domestic product (GDP), in whom it is recognized that RA patient status is substantially poorer than in high GDP countries (49), possibly due in part to poor access to medical services in general and biologic treatments in particular. Nonetheless, even recent data from 2 large United States databases indicated 41% and 60% of patients in moderate or high activity and 25.3 and 12.5% in remission (50), similar to data which had been reported in 2008 (51). Further analysis of this phenomenon appears of interest but is beyond the scope of this study.

Several limitations are seen in this

study. FM was diagnosed according to 1990 criteria in 11 of the 14 comparisons, which depend entirely on the observation of 11 tender points on physical examination, while 3 were based an FM diagnosis on 2010 criteria, which include patient self-report or 2011 criteria which are based only on patient self-report. Tender point counts are correlated strongly with TJC, r = 0.74 (29), and the use of the 1990 criteria may have selected patients with elevated TJC relative to PATGL in elevating DAS28-ESR. Nonetheless, in 2 of the 3 comparisons in which FM was diagnosed according to revised 2010 or 2011 criteria, elevated TJC was seen in FM+ RA patients.

A second limitation is that our search may not have yielded all available reports. However, as noted, the primary goal of this report is to call attention to relatively underrecognized differences between TJC and SJC to elevate DAS28-ESR in RA patients with comorbid FM and thereby clarify interpretation of DAS28 ESR and other indices which include TJC and SJC for clinical decisions, including possible escalation of therapy according to treat-to-target (6). Every identified report indicated that TJC, PATGL, and DAS28 were elevated in FM+ *vs*. FM- RA patients, and a few additional reports with different findings would not alter the conclusions. Third, no information was available concerning possible differences in management in FM+ *vs*. FM- RA patients, which may have resulted from differences in DAS28-ESR. A fourth possible limitation is that only DAS28–ESR was studied, and it is possible that TJC may be less prominent compared to PATGL and SJC in elevations of DAS28-CRP, and particularly SDAI and CDAI, in which TJC and SJC are weighted equally, unlike in DAS28. However, these indices include TJC and PATGL, the 2 measures that explain elevated DAS28 ESR in FM plus patients, and it appears likely that similar findings would be seen with these indices (or any index that includes TJC and PATGL).

In summary, TJC appears to contribute as much as or more than PATGL and far more than SJC or ESR to elevations of DAS28-ESR in FM+ vs. FM- RA patients. This information, along with other reports in the medical literature, may be relevant to possible further revision of RA remission criteria, treat-to-target, and routine clinical patient care. It is feasible in routine care to use a single MDHAQ (multidimensional health assessment questionnaire) to screen for FM according to FAST4 (fibromyalgia assessment screening tool), as well as depression according to MDS2 (MDHAQ depression screen) (44). The findings may be of value to improve monitoring of RA patients in clinical trials, other clinical research, and routine rheumatology care.

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