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Obesity Impacts Swelling of Ankle and Foot Joints in Early Rheumatoid Arthritis Patients

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Abstract

Objective—The evaluation of disease activity in obese rheumatoid arthritis (RA) patients presents challenges particularly in the clinical assessment of swollen joints. This study examines the effect of obesity on the American College of Rheumatology (ACR) core set measures used in assessing RA disease activity with specific focus on the swollen joint count.

Methods—We examined a cross-sectional cohort of 323 early seropositive RA patients (symptom duration ≤15 months). Patients were biologic-naive with ≥6/44 swollen joint count (SJC) and ≥9/44 tender joint count (TJC). ACR core set measures, components of Disease Activity Score 44/erythrocyte sedimentation rate (DAS44/ESR), DAS28/ESR4 item, Clinical Disease Activity Index (CDAI), and body mass index (BMI) were collected. Disease activity measures were compared between BMI categories. Multivariable linear regression models assessed the relationship between high BMI (≥30) and lower extremity (LE) SJC and SJC44 while accounting for other ACR measures.

Results—DAS44/ESR4 item, HAQ-DI, physician global, and SJC44 differed across BMI categories ($p<0.05$). Of the SJC44, metacarpophalangeal joints and LE joints (knees, ankles, metatarsophalangeal joints) were associated with increased swelling in all BMI groups ($p<0.05$). Obesity was significantly associated with LE SJC after adjusting for ACR core set measures.

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Conclusion—There is a direct association between increased BMI and increased swelling of lower extremity joints in RA patients. Increases in DAS44-measured disease activity are higher in obese RA patients due to increased LE swollen joints. DAS28 and CDAI, which emphasize upper extremity joint assessment, are not significantly influenced by obesity.

Key Indexing Terms

disease activity measures; obesity; rheumatoid arthritis

INTRODUCTION

Obesity is a growing concern with nearly 35% of adult Americans reported to be obese in 2011-2014 according to the Centers for Disease Control (CDC). Complications related to obesity result in an estimated annual medical cost of $145 billion. Women have a higher prevalence of obesity than men (36.1% vs. 33.5%), and minorities are more often affected (African Americans, 47.8%; Hispanics, 42.5%) than Caucasians (32.6%) (1).

The literature suggests that obesity increases susceptibility to the development of rheumatoid arthritis (RA) (2-4) and adversely affects RA therapeutic response. Clinical trials often exclude patients above specific weight thresholds. Several studies have shown that overweight and obese RA patients are less likely to achieve remission (5-9), and therapeutic response is lower than for non-obese patients (5, 6, 8, 9). The literature also demonstrates that overweight or obese patients with RA have increased joint deformity, increased functional disability, decreased quality of life, and increased cardiovascular risks (7, 10, 11). Paradoxically, obese RA patients have less radiographic damage despite lower rates of remission and therapeutic response (9).

The American College of Rheumatology (ACR) core set measures were the basis for the development, standardization, and optimization of RA composite outcome measures in the 1990s (12). Few studies have comprehensively analyzed how obesity influences components of RA disease activity measures. The objective of the study reported here was to examine the association between swollen joint count and body mass index (BMI) and other ACR core set measures in the obese RA patient.

METHODS

Patients

We examined a cross-sectional cohort of 323 seropositive early RA patients (<15 months of symptom onset) with poor prognosis recruited from and evaluated by the community practices of the Western Consortium of Practicing Rheumatologists. This cohort has been described in prior publications (13-16). All patients had a diagnosis of RA according to the ACR 1987 criteria, were biologic-naive, and had ≥6/44 swollen joint count (SJC) and ≥9/44 tender joint count (TJC). We categorized BMI based on the standard cut points: <25, 25-30, and ≥30.

Methods

The following characteristics were collected: age, gender, height, weight, disease duration, rheumatoid factor titer, methotrexate use, prednisone use, and erythrocyte sedimentation rate (ESR). Additionally, all components needed to calculate ACR Core Criteria (SJC, TJC, physician global, patient global, acute phase reactants, physical function, pain) and validated RA disease activity measures (DAS44/ESR4 item, DAS28/ESR4 item, and clinical disease activity index [CDAI]) were collected. SJC28, TJC28, SJC44, TJC44, MD global, and patient global are reported on a visual analog scale (VAS). Each patient completed the Health Assessment Questionnaire Disability Index (HAQ-DI). Joints were sub-classified as upper extremity joints (above the waist) or as lower extremity (LE) joints (below the waist). Studies relating to this cohort were approved by appropriate institutional review boards for each of the centers involved.

Statistics

Demographic, clinical, and disease-specific measures were compared among the three BMI groups using chi-squared tests for categorical variables and Kruskal-Wallis tests for continuous variables. Pairwise Wilcoxon rank sum tests between groups were conducted where Kruskal-Wallis tests were significant.

Univariate and multivariable linear regression models were used to assess relationships between high BMI (≥30) and lower extremity SJC and SJC44. The ACR core set measures available for this cohort (patient global, physician global, HAQ-DI, pain, ESR (natural log), and TJC44) were considered as covariates in multivariate models. Pearson correlations among continuous covariates were assessed, and covariates with correlation coefficients greater than 0.5 were not included in the same model due to co-linearity. The final model included BMI ≥30 and ACR core set predictors (excluding HAQ-DI and pain due to collinearity). Statistical analyses were conducted using SAS v3.

RESULTS

Basic Demographics and Disease Characteristics

No statistically significant differences were observed for baseline demographics or for patient disease characteristics across BMI groups (Table 1).

ACR Core Set and Disease Activity Measures

There were no significant differences in ACR core set measures of ESR, patient global, pain, and TJC44 among BMI groups (Table 2); however, physician global, HAQ-DI, and SJC44 significantly differed among the BMI groups ($p<0.05$). Patients with a BMI ≥30 had significantly higher median SJC than patients in the other two BMI groups ($p=0.009$). Patients with a BMI ≥30 had the highest physician global scores of the three BMI groups, and this difference was statistically significant between the high and middle BMI groups ($p=0.03$). Patients with BMI ≥30 also had significantly higher HAQ-DI scores than patients in the middle and low BMI groups ($p=0.02$). Differences in CDAI and DAS28/ESR4 item were not significant (Table 2); however, DAS44/ESR4 item was significantly higher in the highest BMI category than in the other two categories ($p=0.02$).

Swollen Joint Examination

Detailed comparisons were performed for SJC across the BMI categories (Table 2). The overall scores for upper extremity swelling and individual joint swelling for shoulders, elbows, wrists, and proximal interphalangeal joints were not significantly different among BMI groups. The metacarpophalangeal (MCP) SJC was significantly different among BMI groups ($p=0.02$), and was highest among patients within the highest BMI category. The overall scores for lower extremity swelling significantly differed among BMI groups and were highest among patients with high BMI ($p<0.001$). Joint-specific swelling was significantly different across BMI groups for knees ($p<0.001$), ankles ($p<0.001$), and metatarsophalangeal joints ($p=0.01$).

ACR Core Set and BMI Univariate and Multivariate Models

In univariate linear regression models, high BMI was predictive of lower extremity SJC ($p<0.001$) and SJC 44 ($p<0.001$) (Table 3). ACR core set measures patient global, physician global, HAQ-DI, pain, ESR, and TJC44 were considered as potential covariates. Pearson correlations were high between patient global and HAQ-DI ($R = 0.5$, $p<0.001$) and between patient global and pain ($R = 0.8$, $p<0.001$). To prevent co-linearity, HAQ-DI and pain were omitted from multivariate models. Multivariate linear regression models with BMI and ACR core set measures (patient global, physician global, ESR, and TJC44) predicting lower extremity SJC and SJC44 yielded R-square values of 0.40 and 0.58, respectively. BMI was a significant predictor of lower extremity SJC ($p=0.005$) but was not a statistically significant predictor for the total SJC44 ($p=0.10$).

DISCUSSION

In this cross-sectional cohort of 323 early seropositive RA patients, the DAS28 did not show a difference across BMI categories, whereas in obese patients there was an increase in the DAS44, primarily due to an increase in the lower extremity swollen joints counts. Lower extremity pain and tenderness in those with RA and obesity may not be due to RA activity but rather due to dependent edema, osteoarthritis, loss of plantar fat pads, cockup toes, periarticular fat, etc. The DAS28 does not evaluate lower extremities, which may result in under-treatment of the obese patient; or alternatively, the DAS44 may overestimate disease activity in the obese patient since it does evaluate the lower extremities, resulting in over-treatment.

Two previous studies examined the relationship between BMI and 28-joint composite disease activity measures (2, 17). Caplan et al. published a study evaluating 980, approximately 90% male RA patients that suggested that SJC28 performs well in obese male RA patients (17). This study did not examine the joints of the feet or ankles.

In our cohort, the swollen joint counts for MCPs, MTPs, and ankles were higher for obese patients than for patients who are not obese. It is possible that obese RA patients have swollen joint overcalling due to periarticular adiposity or other factors. Silk and colleagues note that “the notion of the standard 70kg patient is outdated” (18), and they suggest physical maneuvers to assist in examination. Others suggest that medial students be trained

to use the “sonoscope” to augment the physical exam (19). In the back clinical hallways, rheumatologists agree that swollen joints (both upper and lower extremities) are difficult to objectively assess in the obese patient. We recently published musculoskeletal ultrasound findings on a cross-sectional small cohort of 43 RA patients (20). We found that obese RA patients had lower overall power Doppler scores, but similar DAS28 and CDAI compared to non-obese patients. We concluded that swollen joints were less likely to represent true synovitis as measured by power Doppler. Further ultrasound studies are needed to fully assess impact of clinically swollen MTPs and ankles in obese RA patients longitudinally with radiographs and/or MRI. On the other hand, the increase in swollen joints we observed in the lower extremities of obese patients may be true synovitis. Research groups have shown that adipokines lead to higher RA disease activity. No study has comprehensively evaluated all aspects of sensitive imaging measures, BMI, clinical disease activity measures, and adipokines.

Several studies have evaluated discordance in composite disease activity measures that exclude the feet and ankles with those measures that do, although not with respect to BMI categories. In a study of 465 RA patients, Bakker et al. reported that the DAS28 underestimates actual disease activity and expected joint damage in recently diagnosed RA patients with disease primarily in the feet (21). Wechalekar et al. evaluated 123 RA patients after 6 months of treatment and showed that more than 20% of patients with ongoing foot synovitis met 28-joint count remission criteria (22). Both groups advocate for regular assessments of the feet and ankles in estimation of RA disease activity for clinical decision-making. How these findings influence treatment decisions of the obese RA patient still remains unclear.

Our study has limitations. This RA cohort was not developed for the purpose of studying the stated objective. Fat composition information was not available, and it is known that BMI is an imperfect measure of obesity. The cohort included active RA subjects as defined by the inclusion criteria, and this could potentially limit the scope of application to general RA population. In addition, this study did not include sensitive imaging data such as magnetic resonance imaging or ultrasound.

Unlike other the ACR Core Set measures, swelling of the lower extremity joints and MCPs, HAQ-DI, and physician global increase with BMI. The elevated swollen joint scores observed among obese patients in our cohort yielded higher DAS44 scores but not higher DAS28 or CDAI. Until further studies delineate the underlying reasons for the higher swollen joint counts in the lower extremities of obese RA patients, we think it is prudent to continue to assess the feet and ankles.

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Table 1

Baseline Demographics and Clinical Characteristics*

	BMI ≤ 25 (N=175)		BMI 25-30 (N=84)		BMI > 30 (N=64)		p-value
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	
Age	48.4	21.2	51.5	18.3	51.2	14.8	0.07
Disease Duration (months)	6.6	6.9	6.0	6.2	4.8	5.5	0.07
RF titer	200.0	393.5	167.5	289.0	215.0	328.0	0.12
	(%)		(%)		(%)		p-value
Female	78.3		72.6		78.1		0.53
Methotrexate use	46.9		46.4		56.3		0.14
Prednisone use	29.7		45.2		43.8		0.80

*IQR = interquartile range, RF = rheumatoid factor, BMI = body mass index

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Table 2

Baseline Disease Characteristics by BMI Group*

	BMI < 25 (L) N=175		BMI 25-30 (M) N=84		BMI ≥ 30 (H) N=64		Kruskal-Wallis p-value	Pairwise Comparisons
	Median	IQR	Median	IQR	Median	IQR		
ACR CORE SET MEASURES								
Patient Global	57	41	53	46	57	38	0.87	
Physician Global	48	37	46	27	55	26	**0.03**	**M<H**
HAQ-DI	1.13	0.88	1.00	1.13	1.38	0.88	**0.02**	**L<H, M<H**
Pain	61	44	61	35	69	43.5	0.35	
ESR	35	28	35	34	40	30	0.65	
Tender 28	12	12	12	10	12	14.5	0.52	
Tender 44	18	15	18	15	19	22	0.60	
Swollen 28	11	11	11	10	14	13.5	0.06	
Swollen 44	16	12	16	14	20	18	**0.009**	**L<H, M<H**
DISEASE MEASURES								
CDAI	32.6	21.0	32.6	15.6	37.2	28.4	0.13	
DAS28/ESR4 item	6.08	1.77	6.15	1.21	6.26	1.71	0.15	
DAS44/ESR4 item	4.47	1.65	4.45	1.78	4.86	2.00	**0.02**	**L<H, M<H**
UPPER EXTREMITIES (UE)								
UE Swollen	11	10	11	10	14	12	0.12	
Shoulder Swollen	0	0	0	0	0	0	0.30	
Elbow Swollen	0	1	0	0	0	1	0.35	
Wrist Swollen	2	1	2	2	2	1	0.16	
MCP Swollen	5	5	5	6	6	6	**0.02**	**L<H**
PIP Swollen	5	6	5	6	5	8	0.56	
LOWER EXTREMITIES (LE)								
LE Swollen	5	7	4	6	8	9	**<0.001**	**L<H, M<H**
Knee Swollen	0	1	0	2	1	2	**<0.001**	**L<H, M<H**
Ankle Swollen	0	2	0	2	2	1	**<0.001**	**L<H, M<H**

	BMI < 25 (L) N=175		BMI 25-30 (M) N=84		BMI ≥ 30 (H) N=64		Kruskal-Wallis p-value	Pairwise Comparisons
	Median	IQR	Median	IQR	Median	IQR		
MTP Swollen	4	6	2	7	7	9	**0.01**	**M<H**

*IQR = interquartile range, BMI = body mass index, HAQ-DI = health assessment questionnaire-disability index, ESR = erythrocyte sedimentation rate, CDAI = Clinical Disease Activity Index, DAS = Disease Activity Score, MCP = metacarpophalangeal joint, PIP = proximal interphalangeal joint, MTP = metatarsophalangeal joint

Table 3

Linear Regression ACR Core Set Measures and BMI Predicting Swelling*

Model Outcome	Predictors	Est.	SE	P-value	R-Square
Lower Extremity Swollen Joint Count	Patient Global	−0.005	0.009	0.592	0.40
	Physician Global	−0.018	0.014	0.194	
	ESR (ln)	0.703	0.310	0.024	
	Tender 44	0.270	0.026	<0.001	
	BMI≥30	1.633	0.570	0.005	
Swollen Joint Count 44	Patient Global	0.018	0.017	0.286	0.58
	Physician Global	0.008	0.025	0.742	
	ESR (ln)	0.701	0.562	0.214	
	Tender 44	0.676	0.046	<0.001	
	BMI≥30	1.765	1.037	0.090	

*BMI = body mass index, ESR = erythrocyte sedimentation rate, ln= natural log, SE= standard error