Overweight and obesity affect clinical assessment of synovitis in rheumatoid arthritis: comparison of ultrasonography and clinical exam

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Abstract

Objective

Body mass index (BMI) might affect rheumatoid arthritis (RA) outcomes. Clinical assessment of swollen joint count (SJC) might also be affected by obesity in terms of obesity-related excess adipose tissue. In this study, we compared ultrasonography (US) and clinical examination in assessing the effect of BMI on RA disease activity assessment.

Methods

This was a single-centre study including RA (ACR/EULAR criteria) patients. US assessment was performed by one trained rheumatologist blinded to clinical data. US synovitis was defined as grey-scale score ≥2 and/or power Doppler score ≥1. The primary outcome measure was difference in SJC (ΔSJC) between clinical and US assessment (US-clinical examination). The secondary outcome was to evaluate the difference between clinical and US assessment of the Disease Activity Score in 28 joints (ΔDAS28) in the 3 BMI subgroups according to the WHO classification.

Results

We included 76 RA patients (mean age 53.8 ± 11.8 years; 67% female). Overall, 28 (36.8%), 33 (43.4%) and 15 (19.7%) were normal weight, overweight and obese, respectively. Baseline characteristics did not differ between the 3 BMI subgroups. US-determined SJC was significantly higher than clinical-determined SJC for overweight and obese RA patients: p=0.001 and p=0.049, respectively. The DAS28 was higher with US than clinical examination within the overweight group only (p=0.002). One-way analysis of variance (ANOVA) revealed a significant difference between ΔDAS28 among the 3 BMI subgroups (p=0.046).

Conclusion

In high BMI RA patients both SJC and DAS28 seem to be undervalued by clinical assessment when compared to US.

Key words

ultrasound, obesity, body mass index, rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a disease characterised by inflammation of joints that could lead to structural damages (1). Obesity, defined by body mass index (BMI) ≥ 30 kg/m^2 (2), is a frequent medical condition, with increased prevalence worldwide (3). Adipose tissue can have immune effects on most of organs through the secretion of adipocytokines (4). This pro-inflammatory condition may contribute to the pathogenesis of inflammatory conditions such as RA. Obesity is associated in some studies with an increased risk of RA (5). The prevalence of obesity in RA patients ranges from 18 to 31% (6, 7). Previous study showed that obesity might have a structural protective impact (8, 9). Obesity could also be associated with severe functional and pain outcomes (10, 11). In obese patients, symptoms related to fibromyalgia are frequent (12) and other painful conditions such as abdominal pain, osteoarthritis or depression are also more frequent in patients with high BMI (13). This obesity-related pain might affect the assessment of RA disease activity. In light of the association of excess adipose tissue and pain score in obese patients, the clinical assessment of swollen joint count (SJC) and RA disease activity measurement might also be affected by obesity. Indeed, periarticular adiposity in obese patients might simulate clinical synovitis, thereby increasing SJC and intensifying treatments. To assess objectively the RA synovitis, imaging procedures such as ultrasonography (US) or magnetic resonance imaging (MRI) are currently recommended (14, 15). Previous studies involving US have demonstrated subclinical joint inflammation in RA leading to increased risk of erosion progression (16-18). It was demonstrated that US had a better reproducibility that clinical exam (19). As a consequence, the DAS28 determined by clinical SJC or by US can be different (20).

The aim of this study was to compare clinical examination and US in assessing the effect of BMI on SJC and the Disease Activity Score in 28 joints (DAS28) in RA patients.

Patients and methods

Patients and study design

We performed a single-centre, cross-sectional, study including subjects with RA, all fulfilling the ACR/EULAR criteria for RA (21). All RA patients were consecutively recruited over 6 months in the rheumatology department of Bichat Hospital (Paris, France). The following data were collected: BMI; gender; age; disease duration; Disease Activity Score in 28 joints (DAS28); pain on a visual analogue scale (0-100 mm); tender joint count and SJC in 28 sites; status of anti-citrullinated peptide antibodies (ACPA) and rheumatoid factor (RF); erosive status; use of disease-modifying anti-rheumatic drugs (DMARDs), corticosteroids or previous biologic agents; erythrocyte sedimentation rate (ESR); and C-reactive protein level. DAS28 was calculated on the basis of ESR. BMI was calculated as weight in kilograms divided by height in square meters. According to the World Health Organisation criteria (WHO) (2), normal BMI was defined as <25 kg/m^2, overweight 25–29.9 kg/m^2, and obesity ≥30 kg/m^2.

The primary outcome measure was difference in SJC (ΔSJC) between clinical and US assessment (US–clinical examination). Secondary outcome was to evaluate the difference between clinical and US assessment of DAS28 (ΔDAS28) in the 3 BMI subgroups according to the WHO classification.

Ethics statement

The local institutional review board (no. 12-011) approved the study, and written informed consent was obtained from all participants.

US assessment

US assessment was performed the same day as clinical examination by one trained rheumatologist who used an Esaote MyLab70 echograph (Genoa, Italy), with linear transducers at 5-12 MHz for shoulders and knees and 12-18 MHz for hands and elbows. The US assessor was blinded to clinical data for patients. All 28 joints were assessed for clinical SJC and calculation of DAS28 for each patient. The grey-scale (GS) score was used to score synovial hypertrophy, and

power Doppler (PD) US was assessed using pulse repetition frequency of 750 Hz with medium wall filter. The colour gain was increased until noise artifacts appeared and then gradually reduced until a flow signal, if present disappeared.

Each joint was assessed in both longitudinal and transverse planes. For shoulders, the bursae and posterior joint cavity were analysed. Radiocarpal, ulnar-carpal and intercarpal wrist joints were analysed, and the highest GS or PD score was used for overall wrist analysis. Knees were studied in moderate flexion (20–30°) on suprapatellar longitudinal and parasagittal planes. Effusion and synovium hypertrophy was combined into an overall GS score as previously described (22). Other joints were analysed according to OMERACT recommendations (23). GS and PD scores were previously defined (24) and determined by using the 0-3 semiquantitative Szkudlarek score (25). Normal subjects have a low GS score (17). US synovitis was defined, as previously mentioned (19), as a GS score ≥2 and/or power Doppler score ≥1. The overall sum of US synovitis scores corresponded to US SJC.

Statistical analysis

Continuous variables are expressed as mean (SD or 95% CI) or median (interquartile range). Categorical variables are expressed as frequencies and percentages. The primary outcome measure was the difference in synovitis between clinical examination and US (US-clinical examination; ΔSJC. Comparison of clinical characteristics between the 3 BMI subgroups was done using Kruskal-Wallis test. Baseline characteristics of each pair of subgroups were also analysed using Mann-Whitney test for quantitative variable and Student's t-test for qualitative variable. A Student's *t*-test was used to test the difference between the 2 examination methods within each group. The existence of a statistically difference between the 3 groups for the ΔSJC was tested with a one-way ANOVA including the BMI group as a unique factor. A *p*-value less than 0.05 was considered as statistically significant.

Table I. Clinical characteristics of all patients with rheumatoid arthritis by body mass index (BMI) subgroups.

	Normal weight BMI <25 kg/m² (n=28)	Overweight BMI 25–29.9 kg/m² (n=33)	Obesity BMI ≥30 kg/m² (n=15)	*p*-value
Age (years), median [IQR]	52 [56-18]	56 [56-16]	53 [54-3.5]	*p*=0.57
Women, n (%)	21 (75.0%)	18 (54.5%)	12 (80.0%)	*p*=0.12
Symptom duration (years), median [IQR]	11.3 [9.5-8.8]	14.2 [12.0-8.0]	9.9 [9.0-5.0]	*p*=0.17
RF positive, n (%)	24 (85.7%)	29 (87.9%)	14 (93.3%)	*p*=0.76
ACPA positive, n (%)	24 (85.7%)	31 (93.9%)	14 (93.3%)	*p*=0.51
Erosive status, n (%)	26 (92.9%)	31 (93.9%)	12 (80%)	*p*=0.27
Steroids use, n (%)	20 (71.43%)	25 (75.8%)	15 (100%)	*p*=0.08
[dose (mg/day), mean±SD]	[6.2 ± 8.3]	[4.1 ± 3.0]	[8.0 ± 3.3]	
DMARDS, n (%)	22 (78.6%)	26 (78.8%)	14 (93.3%)	*p*=0.43
Methotrexate, n (%)	21 (75%)	21 (63.6%)	14 (93.3%)	*p*=0.10
Biologic agent, n (%)	19 (67.8%)	24 (72.7%)	12 (80%)	*p*=0.70
TJC, mean ±SD	3.0 ± 3.8	1.7 ± 2.3	2.1 ±3.7	*p*=0.41
Pain, VAS (0-100), mean ±SD	42.3 ± 30.0	48.2 ± 23.7	57.7 ±21.3	*p*=0.33
ESR (mm), mean ±SD	24.1 ± 23.6	23.7 ± 26.1	20.5 ±19.7	*p*=0.91
CRP (mg/l), mean ±SD	11.2 ± 18.9	13.6 ± 30.9	13.4 ±23.7	*p*=0.88

IQR: interquartile range; RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibodies; CRP: C-reactive protein; DMARDS: disease-modifying anti-rheumatic drugs; TJC: tender joint count; VAS: visual analogue scale; ESR: erythrocyte sedimentation rate.

Table II. Clinical examination and ultrasonography (US) assessment of swollen joint count (SJC) and DAS28) by BMI subgroups.

	Normal weight BMI <25 kg/m² (n=28)	Overweight BMI 25–29.9 kg/m² (n=33)	Obesity BMI ≥30 kg/m² (n=15)	Comparison between groups *p*-value*
SJC				
Clinical SJC, mean ± SD	3.5 ± 3.2	3.1 ± 3.5	2.7 ± 3.1	*p*=0.73
US SJC, mean ± SD	4.0 ± 4.7	4.9 ± 4.3	4.3 ± 6.3	*p*=0.77
Difference in US–clinical SJC, mean ± SD	0.429 ± 3.0	1.818 ± 2.7	1.600 ± 4.0	*p*=0.203
[95% CI]	[-0.739; 1.600]	[0.743; 2.894]	[0.005; 3.195]	
p-value**	*p*=0.467	*p*=0.001	*p*=0.049	
DAS28				
Clinical DAS28, mean ± SD	3.58 ± 1.75	3.29 ± 1.33	3.62 ± 1.42	*p*=0.68
US DAS28, mean ± SD	3.56 ± 1.80	3.46 ± 1.36	3.63 ± 1.54	*p*=0.93
Difference in US–clinical DAS28, mean	-0.014	0.175	0.011	*p*=0.046
[95% CI]	[-0.130; 0.102]	[0.068; 0.282]	[-0.148; 0.169]	
p-value**	*p*=0.812	*p*=0.002	*p*=0.894	

95% CI: 95% confidence interval. **p*-values are from the F-test of one-way ANOVA for comparisons among groups.***p*-values are from Student's *t*-test of a difference between the two measurements within groups.

Statistical analysis involved use of SAS v. 9.2 (SAS Inst., Cary, NC). $p<0.05$ was considered statistically significant. The intra-observer reliability of both SJC assessment procedures was calculated for 10 other RA patients. The intraobserver agreement for US was estimated by the κ coefficient, with agreement scored as >0.8, almost perfect; 0.6–0.8, substantial; 0.4–0.6, moderate, 0.2–0.4, fair, ≤0.2, slight; <0, poor beyond chance.

Results

Patient characteristics

A total of 76 RA patients (67% female, mean age 53.8±11.8 years) were consecutively included (characteristics by BMI subgroup are in Table I). The mean disease duration was 12.3±9.3 years. RF and ACPA were positive for 67 (88.2%) and 69 (90.8%) patients, respectively. Overall, 69 patients (90.8%) showed at least one erosion. At total of 60 patients (78.9%) were taking corticoster-

oids and 62 (81.6%) used DMARDs (methotrexate for 56 [73.7%], mean dose 13.5±9.1 mg/week); 55 patients (72.4%) took biologic agents. According to the WHO classification, 28 had a normal weight, 33 were overweight and 15 were classified as obese. Baseline characteristics did not differ among the 3 BMI subgroups (Kruskal-Wallis test). When BMI subgroups were compared each other, we observed that obese patients are more often treated by corticosteroids than overweight (p=0.044) and normal weight patients (p=0.036). Other variables were not statistically different.

Intra-observer reliability of US and clinical assessment of SJC

The intra-observer variability for clinical and US assessment was calculated for 10 patients with the kappa coefficient and was 0.98 and 0.96, respectively.

Primary outcome: swollen joint count (Table II)

The 3 BMI subgroups did not differ in mean SJC by clinical examination (p=0.73) and US (p=0.77). The mean difference between clinical- and US-determined SJC for patients with normal weight, overweight and obesity was 0.429±3.0 [95% CI -0.739; 1.600], 1.818±2.7 [0.743; 2.894] and 1.600±4.0 [0.005; 3.195], respectively. SJC was significantly higher by US than clinical examination for the overweight group (p=0.001) and obesity group (p=0.049) but not for normal weight group (p=0.467) (Fig. 1). On one-way ANOVA comparing the ΔSJC of the three BMI subgroups, no statistical significance was observed (p=0.203).

The proportion of error between the 2 measures for each joint is detailed in Supplementary Table S1. For all RA patients, the 3 main joints with discordance between US and clinical assessments were knees (25%), wrists (21.71%) and elbows (18.42%).

Secondary outcome: DAS28 (Table II)

Mean DAS28 was similar in the 3 BMI subgroups whatever the modality of assessment: p=0.68 for clinical examination and p=0.93 for US assessment (Table II). The mean difference between clinical- and US-determined DAS28 for patients with normal weight, overweight and obesity was -0.014 [-0.130; 0.102], 0.175 [0.068; 0.282] and 0.011 [-0.148; 0.169], respectively. The DAS28 was higher with US than clinical examination within the overweight group only (p=0.002). One-way ANOVA revealed a significant ΔDAS28 among the 3 BMI subgroups (p=0.046).

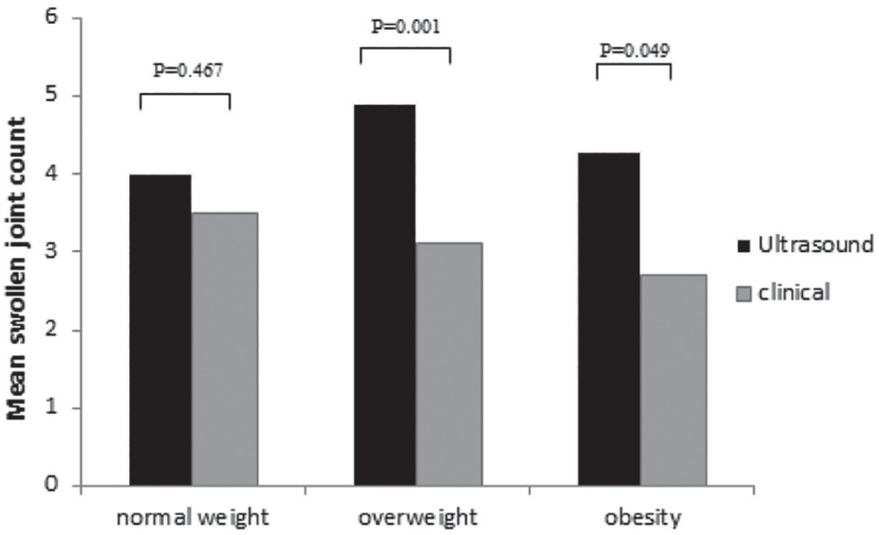

Fig. 1. Ultrasonography and clinical examination of swollen joint count by body mass index (BMI) subgroups.
Normal BMI was defined as <25 kg/m^2, overweight 25–29.9 kg/m^2, and obesity ≥30 kg/m^2.
p-values are from Student's t-test of a difference between the two measurements within groups.

Supplementary Table S1: Proportion of error between ultrasonography and clinical examination for each joint by BMI subgroups

	Normal weight BMI <25 kg/m^2 (n=56)	Overweight BMI 25–29.9 kg/m^2 (n=66)	Obesity BMI ≥ 30 kg/m^2 (n=30)	Total (n=152)
PIP 1	1 (1.78%)	2 (3.03%)	2 (6.67%)	5 (3.29%)
PIP 2	3 (5.36%)	10 (15.15%)	3 (10.00%)	16 (10.53%)
PIP 3	6 (10.71%)	2 (3.03%)	1 (3.33%)	9 (5.92%)
PIP 4	3 (5.36%)	5 (7.57%)	4 (13.33%)	12 (7.89%)
PIP 5	4 (7.14%)	4 (6.06%)	3 (10.00%)	11 (7.24%)
MCP 1	4 (7.14%)	10 (15.15%)	3 (10.00%)	17 (11.18%)
MCP 2	8 (14.28%)	14 (21.21%)	3 (10.00%)	25 (16.45%)
MCP 3	7 (12.5%)	7 (10.61%)	5 (16.67%)	19 (12.5%)
MCP 4	8 (14.28%)	9 (13.64%)	4 (13.33%)	21 (13.81%)
MCP 5	4 (7.14%)	10 (15.15%)	3 (10.00%)	17 (11.18%)
Wrists	12 (21.42%)	16 (24.24%)	5 (16.67%)	33 (21.71%)
Elbows	7 (12.5%)	19 (28.78%)	2 (6.67%)	28 (18.42%)
Shoulders	9 (16.07%)	7 (10.61%)	5 (16.67%)	21 (13.81%)
Knees	16 (28.57%)	16 (24.24%)	6 (20%)	38 (25%)

Data are number (%) of joints for each site.
PIP: proximal interphalangeal joint; MCP: metacarpophalangeal joint.

Discussion

Obesity and adipose tissue could play a role in the development of RA and in the clinical, radiological and treatment response outcomes of the disease (6-10, 26-29). Little is known about the impact of obesity on clinical disease-activity assessment. In this study, we aimed to assess the effect of BMI on RA activity assessment by clinical examination and US. When US was used as gold standard for synovitis assessment, clinical and US assessment of SJC differed for overweight and obese RA groups, particularly for larger joints.

We found a significant difference between clinical and US assessment of DAS28 in only overweight patients.

The relatively small sample of RA obese patients may explain the absence of difference in the particular subset. However, the one way ANOVA provide evidence for a role of high BMI in the undervaluation of the DAS28 by using clinical assessment compared to US: *i.e*. discrepancies (clinical *vs*. US) were statistically correlated with BMI. These results suggest that in RA patients with high BMI, SJC could be missed on clinical examination, leading to undervalue the DAS28. Our data are in good agreement with several studies demonstrating the superiority of US assessment of SJC in RA patients (17, 30-32). However, in those studies, no evaluation of the influence of BMI was performed.

Excess adipose tissue might contribute to the difficulty in clinical assessment of RA, thereby leading to misclassification of synovitis. Among obese RA patients, the joints with a high percentage of error were the larger joints. These results agree with a study showing subclinical synovitis most frequently found in large joints such as the wrist and knee (33). In clinical practice, US assessment may help the clinician evaluate these large joints for which clinical evaluation seems to be difficult. Additionally, US might guide the clinician to decide and perform corticosteroids injection in these large joints.

The relatively low number of obese patients is the main limitation of our study probably leading to the weak effect of BMI on both SJC and DAS28 observed in this particular subset. The SJC accounts for 1.42 although TJC might affect the DAS28 up to 2.96. Moreover, as obese patients had high risk of fibromyalgia (12), the score pain might be affected and DAS28 overestimated. In clinical practice, among those patients with fibromyalgia, the assessment of SJC is the only clinical symptoms being objective. Our study suggests that, in those patients, SJC assessment could be disturbed by adipose tissue. In such situation, US appears to be a relevant tool for SJC assessment. Another limitation could be the absence of radiological assessment. Indeed, previous studies suggested that obese RA patients had a lower risk of radiological progression that those with lower BMI (8, 9). It could be hypothesised that obese RA patients could have more frequently an intensification of their treatment due to high SJC or TJC disturbing the DAS28 calculation. To answer tis question, additional studies in obese patients are required to better assess the impact of high BMI on DAS28 measurement and radiological progression. As tenosynovitis is not included in he DAS25 calculation, we also made the choice to not assess this feature despite the fact that US had a better ability than clinical exam for the detection of tenosynovitis (34). Finally, the absence of interobserver reliability might represent another limitation to the study. The fact that US was performed by one operator did not allow us to determine the interobserver reliability. In our study comparing clinical exam and US, each patient is his own control limiting the importance of measurement of interobserver agreement.

In conclusion, our study is the first to analyse the potential impact of high BMI on SJC and DAS28 measures in RA patients. Our findings suggests that high BMI leads to an underestimation of both SJC and DAS28 in RA patients only clinically assessed, thus supporting the relevance of US examination to better evaluate the activity of RA in high BMI patients.

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