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ORIGINAL ARTICLE

The effect of concomitant hand osteoarthritis on pain and disease activity in patients with rheumatoid arthritis

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Abstract

Introduction Pain is a core complaint among rheumatoid arthritis (RA) patients, and persistent pain requires treatment adjustments according to current strategies. We aimed to quantify the impact of hand osteoarthritis (OA) on health status and residual pain in patients with RA.

Methods This cross-sectional survey compared RA patients with and without osteoarthritis of the hand. The main outcome was pain intensity. Other measurements included disease activity scores (the Disease Activity Score 28-joints; the Simplified Disease Activity Index, SDAI; the Clinical Disease Activity Index, CDAI), functional disability and self-reported quality of life, and the proportion of patients with residual pain (Patient Acceptable Symptom State, PASS).

Results Eighty-one patients were analyzed, including 39 with RA and OA and 42 with RA only. The patients were mainly women (94%), with a median disease duration of 13 years. This group also reported a higher intensity of pain (visual analogue scale, VAS 70 mm vs. 30 mm; $p = 0.003$), higher disease activity (3.89 vs. 2.88; $p = 0.001$), and greater functional disability irrespective of treatment and comorbidities. A strong correlation ($r^2 = 0.69$; $p < 0.001$) between pain and disease activity was observed, although no differences in pain were observed between groups according to disease activity categories. Patients with RA and OA had a higher proportion of residual pain (59% vs. 29%; $p = 0.006$) even in the absence of clinical inflammation.

Conclusion The coexistence of RA and hand OA is associated with distorted disease activity measurements in RA. Osteoarthritis contributes to persistent pain and greater disability in patients with RA.

Keywords Chronic pain · Disability evaluation · Osteoarthritis · Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic condition characterized by stiffness and pain in synovial joints, with a reported prevalence of between 1.0 and 1.5% in our region; the disease mainly affects young women [1]. Most patients with RA present with severe fatigue and irreversible joint damage, leading to impaired functional ability, low productivity, employment loss, increased mortality, compromised emotional well-being, and adverse impacts on quality of life [2–4]. To overcome these adverse outcomes, early and effective treatment is essential to avoid toxicity and substantial strain on global healthcare resources [5–7]; insufficient treatment is linked to persistent pain, disability progression, and other adverse outcomes, some of which may even be life-threatening [8].

Currently, any treatment strategy for RA requires an assessment of disease activity by a validated index, on which all recommendations for additions, adjustments, or changes to medication should be based [9]. Moreover, several indices have been developed to assess the multidimensional impact of RA, including those for measurement of pain, self-perception of well-being, functional ability, social

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relationships, quality of life, accumulated joint damage, the inflammatory state of the disease (also known as disease activity), and remission [10–12]. Despite effective multimodal immunosuppressive therapies, several studies have shown that many patients describe significant pain. Persistent pain has been documented not only in patients with longstanding disease but also in patients with early diagnosed RA who have received adequate treatment [13, 14]. These findings suggest that the mechanisms underlying persistent pain are not directly related to inflammation and that other conditions may contribute to chronic widespread pain in such patients [15, 16]. In this regard, the impact of persistent pain in the RA population and how pain influences inflammatory disease activity measurements considering that other medical conditions may intervene in patient-reported perception have rarely been investigated.

Hand osteoarthritis (OA) is a highly prevalent condition and the most common form of OA [17]. OA is a heterogeneous disease that may involve multiple joints and has several patterns of presentation, but its hallmark is the presence of nodes in both distal and proximal interphalangeal joints [18]. The presence of symptomatic hand OA is associated not only with poor quality of life and increased functional disability but also with depression, anxiety, and negative perceptions of patients regarding their disease [19]. Although the high frequency of hand OA is broadly recognized, the coexistence of this condition in RA and its impact on RA have not been fully studied. Moreover, the possible effects that hand OA may have on disease activity measurements, persistent pain, and self-reported health status are not well known. To overcome these concerns, we aimed to investigate the pain characteristics of patients with both RA and hand OA to describe the effects of hand OA on disease activity, self-reported health status, and the frequency of persistent pain in patients with RA and to compare this group with patients without hand OA.

Patients and methods

Patients

For this study, participants older than 18 years with an RA diagnosis were enrolled [20, 21]. Then, a search was conducted for a concurrent diagnosis of hand OA [22]. The exclusion criteria comprised any additional inflammatory joint disease or autoimmune illness, a previous or concurrent diagnosis of fibromyalgia or other widespread chronic pain syndromes, a history of cancer, an inability to read/write, current use of opioid drugs for pain relief, severe mental illness, moderate or severe cognitive impairment, or the use of psychotropic drugs (e.g., lithium) other than mild antidepressant drugs or low-dose benzodiazepines for mild sleep disorders. All patients signed an informed consent form, and the institutional review board on human research and the local ethics committee (Comité de Ética en Investigación, CONBIOETICA-09-CEI-007-20180529) approved the study.

Methods

Patient data were collected during a one-time visit. Information related to demographics, comorbidities, and disease characteristics were recorded. Previous diagnoses of depression and/or anxiety disorders, as well as sleep disorder defined as an impairment of the ability to initiate or maintain sleep (Code G47.0, International Classification of Diseases-10), were also recorded based on diagnoses established in the electronic clinical charts used in our setting. We performed a complete assessment of disease activity using four different scores: the Disease Activity Score 28-joints with erythrosedimentation rate (ESR) (DAS28-ESR), DAS28-C-Reactive Protein (DAS28-CRP), the Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI). We divided all patients into four categories according to the DAS28 cut off points [23]. Briefly, the categories were remission (≤ 2.6) and low (> 2.6 and ≤ 3.2), moderate (> 3.2 and ≤ 5.1), and high (> 5.1) disease activity. Functional disability was measured with the Health Assessment Questionnaire Disability Index (HAQ-Di) Spanish version [24], and health-related quality of life was measured with the RA Quality of Life (RAQoL) questionnaire [25, 26]. Pain was evaluated by a visual analogue scale (VAS) where patients rated pain on a 100-mm scale between "no pain" (a score of 0) and "worst possible pain" (a score of 100). Furthermore, the patients indicated a global assessment of their health related to RA on a VAS, where 0 was "the best state of health related to RA," and 100 was "the worst state of health related to RA." The patients' treating physicians also rated patient global assessments on a 100-mm VAS. Finally, pain scores were qualified using the concept of the Patient Acceptable Symptom State in Pain (PASS) scale and were defined as the symptom scores beyond which patients consider themselves well, reflecting the concept of "feeling well" [27, 28].

Analysis

Descriptive statistics were determined for all data. For categorical variables, the X^2 test (or Fisher's exact test when appropriate) was used. As the distribution of pain intensity was non-normal, we conducted a Mann-Whitney U test to compare continuous covariates and Spearman's rho test to analyze correlations. We required 35 patients per group to identify a clinically significant difference of 15 mm on the pain VAS, with an alfa of 0.05 and 80% power. The software employed was IBM/SPSS V.23.

Results

A total of 81 patients were enrolled, including 39 with RA but no hand OA (group 1) and 42 with both RA and hand OA (group 2). The main demographic characteristics are depicted in Table 1. Patients with RA and hand OA were significantly older ($p = 0.012$). The median disease duration was 13 years, and no differences in the positivity of rheumatoid factor (RF) or anticitrullinated protein autoantibodies (ACPA) were observed. Mood and sleep disorders were present in the same proportions in both groups.

As shown in Table 2, no differences were found between the groups regarding treatment in terms of the proportions of methotrexate, biologic agents, and corticosteroid use, although the patients in group 2 showed a trend towards more frequent usage of nonsteroidal anti-inflammatory drugs (NSAIDs) (78.5% vs. 92.6%, $p = 0.06$). Furthermore, the impact of OA coexistence in patients with RA was better reflected in the perceptions of pain and global well-being. Patients with OA suffered a greater intensity of pain and had both poor self- and physician-reported perceptions of health status and greater functional disability. Self-reported quality of life was similar in both groups. We did not find such differences after comparing patients with and without diabetes and patients with and without high blood pressure.

Patients with OA disclosed a higher intensity of pain than those without OA (70 mm vs. 30 mm, $p = 0.003$). Additionally, pain scores were closely related to the number of tender joints, functional disability, and patient or physician global assessments in both groups (Table 3). Nevertheless, group 2 patients had a greater number of swollen joints, as indicated previously, but no correlation was found between this item and pain scores. Moreover, while the patients in this group were older, age was not associated with pain intensity. When the pain intensity was stratified by comorbidities, a higher intensity of pain was observed across hypertensive and menopausal patients with OA than among patients without OA, 31 vs. 62 mm ($p = 0.015$) and 36 vs. 59 mm ($p = 0.006$), respectively. We found no such difference among diabetic patients, 34 vs. 54 mm ($p = 0.56$). Because both the swollen joint count and global health score were higher in group 2, all indices for the measurement of disease activity were higher in these patients. Thus, a positive relationship between pain intensity and disease activity was noted (Fig. 1); these differences remained when serum CRP was included instead of the ESR in the DAS28 equation or with the disease activity assessment by using the SDAI or the CDAI, which does not require any laboratory biomarker analysis.

We compared the impact of hand OA on pain scores stratified by disease activity (Fig. 2). We found no differences between the groups (with and without OA) in any disease activity category, although the pain scores of patients with a high disease activity level were significantly higher than those in all other groups ($p < 0.001$), similar to the patients in the moderate activity stratum ($p < 0.001$) (Fig. 2).

Regarding residual pain, two-thirds (59%) of the patients without hand OA patients achieved the PASS compared with less than one-third (29%) of the patients with hand OA, $p =$

Table 1 Demographic characteristics and comorbidities of RA patients with and without OA

	RA without OA ($n = 39$)	RA with OA ($n = 42$)	P value[¶]
Age (years [median, IQR])	57 (47–65)	60 (55.8–74.2)	0.012*
Gender, *n* (% of females)	35 (89.7)	41 (97.6)	0.19
Age at diagnosis (years [median, IQR])	42 (34–50)	48.5 (35–57)	0.075
RA duration (years [median, IQR])	13 (5–23)	13 (7–24.3)	0.57
Body mass index (kg/m^2 [median, IQR])	25.7 (23.2–27.7)	25.7 (24–28.6)	0.48
Current or ever smoker, *n* (% of yes)	5 (12.8)	5 (11.9)	1.0
Type 2 diabetes mellitus (% with)	3 (7.7)	11 (26.2)	0.028*
Systemic high blood pressure (% with)	9 (23.1)	20 (47.6)	0.021*
Menopause, *n* (% yes)	26 (66.7)	36 (85.7)	0.043*
RF, *n* (% of positive)	34 (87.2)	31 (73.8)	0.16
ACPA, *n* (% of positive)	15 (38.5)	17 (40.5)	0.85
Depression diagnosis, *n* (%)	6 (15.4)	6 (14.3)	0.88
Anxiety diagnosis, *n* (%)	2 (5.1)	2 (4.8)	1.0
Sleep disorder, *n* (%)	20 (51.3)	14 (33.3)	0.1

The significance is written in each of the cells. The asterisks point that the value is significant P<0.05.

Continuous variables are expressed as the median (25th–75th quartiles)

[¶] Chi-squared or Fisher's exact tests were used for discrete variables, and the Mann-Whitney test was used for continuous variables. *IQR*, interquartile range; *RA*, rheumatoid arthritis; *RF*, rheumatoid factor; *ACPA*, anti-citrullinated protein antibodies

Table 2 Comparison of disease activity, treatment, disability, and quality of life between patients with and without OA

Item	RA without OA ($n = 39$)	RA with OA ($n = 42$)	P value[¶]
Tender joint count	0 (0–2)	1 (0–2.25)	0.08
Swollen joint count	0 (0–0)	3 (0–5)	< 0.001*
ESR, mm/h	33 (21–42)	28 (17–42.5)	0.09
CRP, mg/dl	0.7 (0.3–2.6)	0.6 (0.1–2.23)	0.28
Pain intensity, VAS, mm	30.0 (7.0–70.0)	70.0 (35.0–81.3)	0.003*
Patient's global assessment VAS, mm	15 (7–50)	50 (20–76.3)	0.003*
Physician's global assessment VAS, mm	10 (5–20)	20 (10–38.5)	0.002*
DAS-28 ESR	2.88 (2.4–3.9)	3.89 (3.2–4.4)	0.001*
DAS-28 CRP	1.97 (1.1–2.5)	3.29 (2.7–4.0)	< 0.001*
SDAI	8.2 (2.6–12.6)	12.3 (5.9–21.3)	0.005*
CDAI	4 (2–9.6)	10 (5.0–14.1)	0.001*
Methotrexate use, *n* (%)	8 (21.4)	9 (21.4)	0.8
Steroid use, *n* (%)	15 (38.5)	14 (33.3)	0.63
Biological treatment, *n* (%)	2 (12.8)	6 (14.3)	0.84
NSAID use, *n* (%)	33 (78.6)	36 (92.3)	0.08
HAQ-Di score	0.15 (0.1–1.0)	0.82 (0.3–1.56)	0.01*
RAQoL score	6.0 (2.0–20.0)	10.5 (5.5–17.3)	0.32

The significance is written in each of the cells. The asterisks point that the value is significant P<0.05.

Continuous variables are expressed as the median (25th–75th quartiles).

[¶] Chi-squared or Fisher's exact tests were used for discrete variables, and the Mann-Whitney test was used for continuous variables. *ESR*, erythrocyte sedimentation rate; *CRP*, C-reactive protein; *VAS*, visual analogue scale; *DAS*, disease activity index; *SDAI*, simplified disease activity index; *CDAI*, clinical disease activity index; *NSAID*, non-steroidal anti-inflammatory drug; *HAQ-Di*, health assessment questionnaire disability index; *RAQoL*, rheumatoid arthritis quality of life questionnaire

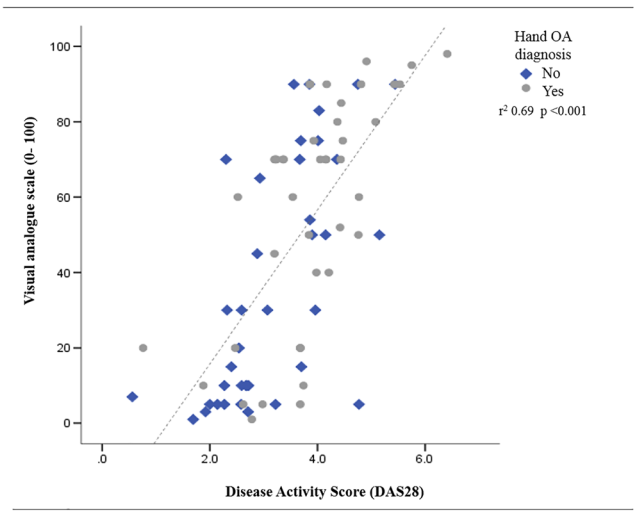
0.006 (Fig. 3). According to these observations, a higher proportion of patients with persistent pain were found among those with both conditions, RA and hand OA, highlighting the impact of the latter diagnosis on the perception of well-being in those patients who suffer from both conditions.

Table 3 Correlations between pain intensity and age, disease characteristics, functional disability and self-reported quality of life

	Pain intensity	
	RA without OA	RA with OA
DAS28	0.63 ***	0.69 ***
Disease duration	0.1	0.06
Age at survey	− 0.13	− 0.24
Number of tender joints	0.49 ***	0.42 **
Number of swollen joints	0.36 *	0.18
Patient global assessment	0.84 ***	0.88 ***
Physician global assessment	0.64 ***	0.64 ***
HAQ-Di	0.64 ***	0.58 ***
RAQoL	0.67 ***	0.57 ***

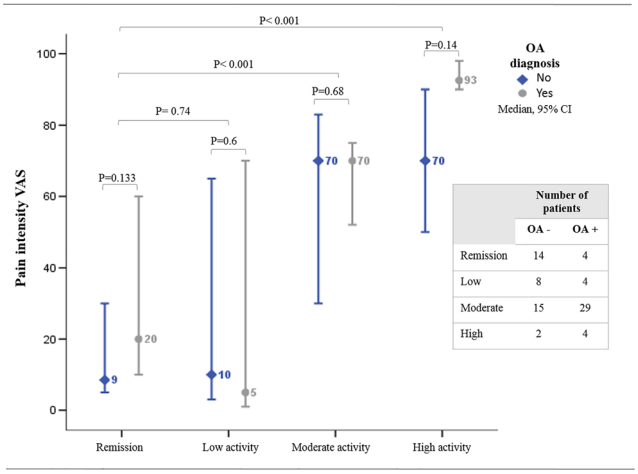
RA, rheumatoid arthritis; *OA*, osteoarthritis; *DAS*, disease activity score; *HAQ Di*, health assessment questionnaire disability index; *RAQoL*, rheumatoid arthritis quality of life questionnaire

The numbers represent linear Spearman's coefficients, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$



Note: OA: osteoarthritis; r²: Spearman coefficient

Fig. 1 Association between intensity of pain and severity of disease activity in patients with RA



VAS: visual analogue scale. P values stand for comparisons between categories of disease activity and between OA-/OA+ patients in each category tested by Wilcoxon test.

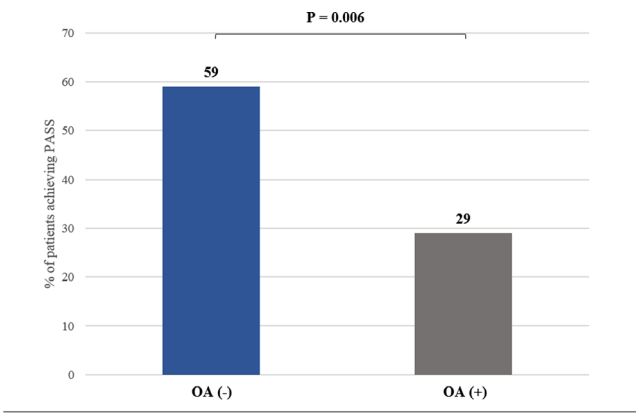
Fig. 2 Differences of pain intensity in patients with RA in four categories of disease activity with and without hand OA

Discussion

Our findings demonstrate that the coexistence of OA in patients with RA generates important consequences in several aspects of their lives; additionally, these patients might be considered as a different population. Inoue et al. suggested that patients with late-onset RA might have a unique susceptibility to articular damage related to previous OA changes. They found that patients with both conditions presented with a larger number of painful joints and higher pain scores despite similar disease durations and adequate treatment and that these features might be related to degenerative changes unrelated to RA [29]. Our patients with RA only were younger that those with both illnesses, thus supporting this idea; unfortunately, we were not able to determine whether an OA diagnosis was established after the RA diagnosis.

Both physicians and patients often consider that pain in RA is attributable to active inflammation; nevertheless, patients may experience discomfort or pain without having inflammation, even in the sites of previous episodes of arthritis, in joints with structural damage, or due to other causes [30]. We showed that the presence of OA predicts a higher intensity of pain and a poorer global assessment by the patient, although physicians' perceptions differ, assigning lower scores for global assessments when inflamed joints are not detected [31]. The measurement of RA disease activity in patients with OA could be distorted and biased towards higher scores and a lower probability of being in a state of well-being, referred to as "feeling good," through the PASS [27], with a cut off value of 40 mm [28]. Regardless of the index used to assess disease activity, i.e., the DAS28, DAS28-CRP, SDAI, or CDAI, with or without the inclusion of serum biomarkers, a notable proportion of patients did not achieve the PASS when OA was present. Differences in pain intensity influence the assessment of disease activity according to the number of painful joints, which is usually determined by asking a patient if pain is present when a joint is touched or squeezed, a maneuver that is clearly patient dependent. Additionally, the state of a patient's health is usually determined by the sensation of pain. In this group of patients, these indices overestimate disease activity; in contrast, previous reports in younger patients with RA indicate that these indices seem to underestimate disease activity [32, 33]. Therefore, in some specific populations, disease activity measurement indices may require an adjustment in the equation, with different weights for each included variable, reflecting the rationale for using several indices because pain and/or painful joints are weighted differently.

On the other hand, treatment decisions in RA should be supported by a pooled index that includes at least articular counts and the patient's global perception of health [34]. In the treat-to-target strategy, either using index scores as a continuous scale or disease activity intervals or categories, such scores must support disease-modifying antirheumatic drugs (DMARDs) additions or changes [35]. Further, in the specific population of patients with OA, these changes might be related to the use of more drugs or higher doses than required to maintain disease remission or low disease activity rather than determining an optimal and multimodal strategy for pain management [30]. In this regard, the treating physician's experiences may be helpful for individual patients considering that the prescription process is a complex intellectual task, which minimally includes analysis of previous experiences and recognition of individual characteristics of the disease, the clinical course, pain, well-being, accumulated articular and systemic damage, and comorbidities. Our findings suggest that activity indices must be adjusted by diminishing the items with greater subjectivity and variability, such as those influenced by pain as evaluated elsewhere using the EULAR response criteria for determining remission [36]. Belmonte-Serrano performed a theoretical exercise to determine the



P value after testing proportions by X^2 test.

Fig. 3 Comparisons of RA patients with and without hand OA who achieved the patient acceptable symptom state (PASS)

contribution of each DAS28-isolated component and found an increase of 0.56 units with two painful joints and 0.79 with three painful joints, as well as 0.62 units above a VAS score of 40 mm for the perception of health status, which is above the PASS [37]. This finding reinforces the implications of having a chronic noninflammatory condition when physicians assess pain intensity and self-reported composite measurements in patients with RA.

Type-2 diabetes mellitus (DM2) and metabolic syndrome have been proposed as modern-day factors in the pathogenesis of OA. A study found that hand OA is associated with metabolic syndrome even after controlling for body weight [38]. Interestingly, people with high blood pressure have an increased risk of hand OA independent of obesity, and the prevalence of OA is higher in patients with DM2 than among patients without diabetes [39, 40]. Our results seem to confirm these observations based on the comparison of pain scores between patients with and without hand OA by comorbidity strata. Regarding psychiatric conditions, pain intensity attributable to hand OA had no effect, as we did not observe differences in the frequency of such conditions in the RA with OA group.

Our study has some limitations. First, we included a small number of participants from only one center in a single geographical area, which may influence the differences in some of the analyses (e.g., quality of life) or the differences due to comorbidities. Thus, these findings must be interpreted with caution when trying to generalize them. The cross-sectional design also prevented further analysis of factors associated with variations or increases in pain perception, although the most common psychiatric conditions showed no direct impact between groups. Second, including an additional control group of patients with "primary" OA (without RA) may have revealed valuable information regarding the contribution of a noninflammatory chronic disease to health status in patients without any other rheumatic disease. However, as the aim of this study was to explore the effects of OA on patients with RA even beyond the inflammatory state, we did not include this third group. Finally, because we used the ACR clinical definition for hand OA to classify the patients, we did not differentiate between erosive and nonerosive OA in patients with RA, which is important, as many patients with erosive OA could potentially be misclassified as having RA. Nevertheless, erosive OA is easily distinguished from RA by the absence of RF and ACPA and the absence of prolonged morning stiffness and a normal ESR/CRP level [41], which all of our patients had at the time of the assessment.

In summary, we found that hand OA in a cohort with RA has important impacts due to higher intensity of pain, affecting patients' functional ability in activities of daily life as well as their own perceptions of health. OA also causes increases in disease activity scores and is therefore an important factor in residual pain, possibly resulting in the exposure of patients to potentially harmful treatments rather than pain management alone.

Compliance with ethical standards

Ethical approval All procedures in studies involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approval was granted by the Local Bioethics Committee for Research (Comité de Ética en Investigación, CONBIOETICA-09-CEI-007-20180529).

Informed consent Informed consent was obtained from all participants included in the study.

Disclosures None.

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