

# The impact of depression and anxiety on pain reported by patients with rheumatoid arthritis undergoing treatment

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**ABSTRACT.** This study analyzed the joint pain of 46 patients with rheumatoid arthritis (RA) undergoing treatment with disease-modifying antirheumatic drugs (DMARD), for at least one year, and evaluated by pain intensity numeric scale and by the McGill Pain Questionnaire (MPQ), anxiety and depression by the Hospital Anxiety and Depression Scale (HADS). We compared them with 46 patients without RA matched by age and sex. We also examined the relationships between anxiety and depression and pain intensity, disease activity and physical dysfunction accessed by the Rheumatoid Arthritis Disease Activity Index (RADAI) and the Health Assessment Questionnaire (HAQ), respectively. Most patients with RA, 93.5%, continued to report joint pain and had higher pain intensity and higher scores in all domains of the McGill Pain Questionnaire (MPQ) than 58.7% of the 46 patients without RA with joint pain. Patients with RA were more likely to have depression defined by HADS $\geq$ 11 than the controls but the association was non-significant when adjusted for the presence of pain. The median score of anxiety symptoms was significantly higher in patients with RA than in those without RA. There was an association of depression and a positive significant correlation of anxiety symptoms with higher intensity of pain, disease activity and physical dysfunction. There was no difference between patients with RA and depression and without depression on the sensory domain and in the total MPQ score. Otherwise, there was a moderate significant correlation of the levels of anxiety with all pain domains of the MPQ, except the sensory one. In conclusion, pain remains a prevalent symptom in RA patients despite treatment. More studies are necessary to verify if the qualitative assessment of pain could be used to evaluate the influence of anxiety and depression on pain reported by these patients.

**Keywords:** Arthritis; anxiety disorder; depressive disorder; arthralgia.

Received on March 17, 2022

Accepted on January 10, 2023

## Introduction

Rheumatoid arthritis (RA) is an inflammatory, chronic, systemic and autoimmune disease that mainly affects the synovial joints, but often evolves with extra-articular involvement and comorbidities, especially cardiovascular diseases (Smolen, Aletaha, & McInnes, 2016). This disease affects 0.5 to 1% population, is two to three times more common in women, and can affect any age group, but with a peak incidence approximately at 50 years of age (van der Woude & van der Helm-van Mil, 2018).

In recent decades, there has been a significant change in the clinical follow-up of RA, with the establishment of new classification criteria, the development of disease-modifying antirheumatic drugs (DMARDs) and new treatment strategies. The latter include a more objective assessment of disease activity, using composite indices such as the Disease Activity Score in 28 Joints (DAS-28), which includes the count of swollen and painful joints, the patient's overall assessment of health and inflammatory markers, such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) (Anderson, Zimmerman, Caplan, & Michaud, 2011).

Although these advances have made it possible to substantially improve the inflammatory markers and the number of swollen joints, it has been observed no significantly better parameters reported by patients, such as joint pain and global health assessment (Gullick et al., 2019).

Experimental studies have shown that inflammatory cytokines act directly on peripheral and central neurons, leading to their hyperexcitability that persists despite inflammation control (Vazques et al., 2012; König, Zharsky, Möller, Schaible, & Ebersberger, 2014; Heisler et al., 2020). Additionally, repeated exposure to inflammation (Bell et al., 2017) and chronic pain (Hilderink, Burger, Deeg, Beekman, & Voshaar, 2012) are risk factors for developing depression.

In this sense, there is evidence accumulated in recent years of a higher prevalence of anxiety and depression in patients with RA than in the general population (Sturgeon, Finan, & Zautra, 2016). In patients with RA, anxiety and depression are associated with increased perception of pain that can be caused by increased inflammatory cytokines due to lack of adherence to treatment and/or psychological stress and depression (Vallerand, Patten, & Barnabe, 2019). Studies on biological drugs in RA that evaluated depression as a secondary outcome have shown an important antidepressant effect of these drugs compared to placebo (Kappelman, Lewis, Dantzer, Jones & Khadanker, 2016). Moreover, the use of non-steroidal anti-inflammatory drugs has been shown to be beneficial in patients with depression even without associated comorbidities (Köhler et al., 2014).

However, physical inactivity and the consequent reduction in endorphin levels and a negative cognitive bias associated with depression, can also contribute to an unfavorable assessment of joint pain and overall health or disease by the patient (Rathbun, Reed, & Harrold, 2013), resulting in a high total disease activity score that would erroneously indicate the combination or switch of DMARDs (Heisler et al., 2020).

Thus, the need for better pain assessment in patients with RA has been highlighted. But there are still few studies that have evaluated the qualitative correlation between pain and depression and anxiety in RA. Using the McGill Pain Questionnaire (MPQ), Noda, Saitou, Matsushita, Ukishi, and Kurosaka (2022) observed that, in patients with RA, the main descriptors according to severity of central pain sensitization were “sharpening” and, “stabbing”, and according to disease severity, “throbbing” and “tender”; and the authors suggest that patients with symptoms of anxiety and depression would be among those with central sensitization. Another study showed that women with fibromyalgia have higher scores in the evaluative pain component of the MPQ than those with RA and more frequently describe the pain as tender, aching, burning and spasm; and that this difference is mainly influenced by depression and the extent of pain (Burckhardt, Clark, & Bennet, 1992).

Therefore, this research aimed to observe whether symptoms of anxiety and depression are more frequent in patients with RA undergoing treatment, for at least one year, with DMARD than in people without RA; compare, between these two groups, the level of joint pain by numerical scale and by measuring the sensory, affective, evaluative and miscellaneous components of pain using the McGill Pain Questionnaire (MPQ) (Main, 2016); as well as to evaluate the correlation between anxiety and depression and joint pain, disease activity and physical dysfunction in RA patients undergoing treatment.

## Material and methods

This was a case-control study that compared consecutive patients followed up at the outpatient clinics of the local University Hospital (UH), who met the 2010 *American College of Rheumatology – European League Against Rheumatism* (ACR-EULAR) classification criteria for RA (Aletaha et al., 2010) and who had been on DMARD treatment for at least one year, and individuals who did not meet these criteria, matched for age and sex, who were recruited among residents of places close to the patients' residence, employees of the UH, University and public schools. People <18 years of age and indigenous people were excluded. All participants expressed their consent by signing the Informed Consent (IC) in person, respecting safety protocols during the 2019 Coronavirus disease (COVID-19) pandemic. The project was approved by the Research Ethics Committee involving human beings of the local Federal University, CAAE:30044920.4.0000.5160.

Demographic and clinical data were collected after face-to-face and online training for the researchers. The interviews were carried out via WhatsApp, the responses were deleted after registered, through a structured online questionnaire on Google Forms, in which the participants were identified by codes previously assigned to each.

The duration of illness and treatment, the drugs used and positivity for rheumatoid factor (RF) and for antibodies against cyclic citrullinated peptides (anti-CCP) were collected through review of medical records.

The cut-off point for schooling was  $\geq 12$  years of study. People considered diabetic, hypertensive, with dyslipidemia and with thyroid problems were those who reported having a medical diagnosis and/or being on medication to treat these diseases. Weight (kg) and height (m) were also self-reported and body mass index (BMI) was calculated using the formula:  $BMI = weight/height^2$ . Individuals considered smokers were those who stated that they were currently smoking and who smoked regularly, defined as  $\geq 5$  cigarettes per week on most weeks, (Elbejjani et al., 2019), and former smokers were those who smoked cigarettes regularly, but who they had not had this habit for over a year.

The presence of joint pain was considered for participants who answered “yes” to the question “Have you felt pain in any joint in the last seven days?” To assess the level of joint pain, a numeric pain scale from zero to ten was used, where zero represents no pain and ten the worst pain imagined by the patient. Pain was also assessed using the McGill Pain Questionnaire (MPQ) (Main, 2016), translated and adapted for Brazil (Pimenta & Teixeira, 1996), which consists of 78 pain descriptors categorized into 20 groups that assess the painful experience in the sensory, affective, evaluative and miscellaneous dimensions of pain. For this study, we used the pain index resulting from the sum of the intensity values attributed to the descriptors chosen by the patients in each domain and the total score, which is the sum of all domains (Pimenta & Teixeira, 1996; Main, 2016).

The *Hospital Anxiety and Depression Scale* (HADS) (Zigmond & Snaith, 1983; Faro, 2015) was used to assess the level of anxiety and depression; those who scored  $\geq 11$  on the respective scales were considered with diagnosis of anxiety or depression (Covic et al., 2012). Physical dysfunction was assessed by the *Health Assessment Questionnaire* (HAQ), translated and validated for Brazil (Ferraz, Oliveira, Araujo, Atrá, & Tugwell, 1990), and disease activity by the *Rheumatoid Arthritis Disease Activity Index* (RADAI) (Anderson et al., 2011). Continuous variables were expressed as mean and standard deviation (sd) or median and interquartile range (IQ), and categorical variables as absolute numbers (n) and percentages (%). Continuous variables were compared using Student's t-test or Mann-Whitney test and categorical variables using Chi-square or Fisher's exact tests. The odds ratio (OR) and the 95% confidence interval (95%CI) were determined by logistic regression for each categorical variable that resulted significant in the comparison between groups and were included in a multivariate logistic regression model when appropriate. Correlations between anxiety and pain levels, disease activity and physical dysfunction were estimated using Spearman's correlation coefficient. The two-tailed significance level was  $p < 0.05$ .

## Results

We evaluated 92 participants, 46 of whom met the 2010 ACR-EULAR classification criteria for RA (RA group) and 46 who did not meet these criteria (non-RA group). Each group was composed of 87% females and 13% males. The mean age was 55.22 ( $\pm 7.02$ ) years in the RA group and 55.25 ( $\pm 8$ ) years in the non-RA group,  $p = 0.99$ .

The mean disease duration of RA patients was 15.80 ( $\pm 7.86$ ) years. All in the RA group were using the following conventional DMARDs for at least one year: 52.17% with methotrexate, 36.96% with leflunomide and 10.87% with sulfasalazine combined with hydroxychloroquine. Furthermore, 71.74% were also using biological DMARDs. Half of the patients were RF and 12 (26.09%) anti-CCP positive, but 10 (21.74%) had not undergone this last exam.

The two groups did not differ statistically in terms of self-reported color, marital status, schooling, unemployment and retirement. However, significantly fewer patients in the RA group than in the non-RA group were working for pay (34.8% vs. 63%,  $p = 0.012$ ) (Table 1).

**Table 1.** Demographic characteristics of participants with and without Rheumatoid Arthritis (RA).

Variables		With RA (46) n (%)	Without RA (46) n (%)	<i>p</i>
Self-reported color	White	24 (52)	28 (60.9)	0.53
	Non-white	22 (47.8)	18 (39.1)	
	Single	4 (8.7)	7 (15.2)	
Marital status	Married or in a stable union	30 (65.2)	29 (63)	0.60
	Divorced or widowed	12 (26.1)	10 (21.7)	
Schooling	<12 years of education	32 (69.6)	27 (58.7)	0.55
	$\geq 12$ years of education	14 (30.4)	19 (41.3)	0.38
Working for pay <sup>a</sup>		16 (34.8)	29 (63)	0.012
Unemployed <sup>a</sup>		13 (28.3)	7 (15.2)	0.21
Retired or with sick pay		13 (28.26)	8 (17.4)	0.32

<sup>a</sup>Patients who reported being “housekeepers” and therefore did not consider themselves unemployed were not included.

RA and non-RA groups were statistically similar in terms of mean BMI [28.57 ( $\pm 6.27$ ) kg/m<sup>2</sup> vs. 28.22 ( $\pm 5.89$ ) kg/m<sup>2</sup>,  $p = 0.81$ ], diagnosis of systemic arterial hypertension (54.3% vs. 43.5%,  $p = 0.40$ ), diabetes (17.4% vs. 15.2%,  $p = 1.0$ ), dyslipidemia (19.6% in both groups,  $p = 1.0$ ) and thyroid problems (23.9% vs. 19.6%,  $p = 0.8$ ). In both groups, 2 (4.3%) people were smokers,  $p = 1.0$ . However, 17 (37%) and 6 (13%) were former smokers in the RA and non-RA groups, respectively,  $p = 0.016$ .

Patients in the RA group had a higher median anxiety score than those in the non-RA group [7 (5-10) vs. 6 (2.25-8),  $p = 0.034$ ]. There was no significant difference between the two groups regarding the depression

score and the diagnosis of anxiety using the HADS (Table 2). Diagnosis of depression was higher in the RA group than in the non-RA group (26.09% vs. 8.7%,  $p=0.05$ ). In the RA group, 7/12 (58.33%) patients with depression also had anxiety.

**Table 2.** Assessment of anxiety and depression using the Hospital Anxiety and Depression Scale in groups with and without Rheumatoid Arthritis (RA).

Variables	With RA (46) median (IQ <sup>a</sup> )	Without RA (46) median (IQ <sup>a</sup> )	<i>P</i>
Anxiety score	7.00 (5-10)	6.00 (2.25-8)	0.034
Depression score	6.50 (3.25-10.75)	6.00 (3-8)	0.42
	<i>n</i> (%)	<i>n</i> (%)	
Anxiety(HADS <sup>b</sup> ≥11)	9 (19.6)	6 (13)	0.40
Depression(HADS <sup>b</sup> ≥11)	12 (26.09)	4 (8.7)	0.05

<sup>a</sup>Interquartile range. <sup>b</sup>Hospital Anxiety and Depression Scale.

Joint pain was reported by 93.5% patients in the RA group and by 58.7% non-RA patients, OR=10.86, 95% CI=2.72-37.36,  $p=0.0005$ . It was attenuated when adjusted for the presence of depression, but remained significant, OR=8.54, 95% CI=2.25-32.33,  $p=0.0016$ . Among people who reported joint pain, the median pain intensity was 7 (5-8) and 4 (2.5-6.5), respectively, in the RA and non-RA groups,  $p=0.004$ . Patients with RA and pain had significantly higher scores in all pain quality domains and in the total MPQ score than people without RA and with joint pain (Table 3).

**Table 3.** Assessment of pain quality by the McGill Pain Questionnaire in participants with and without Rheumatoid Arthritis (RA) and with joint pain

Variables	WithRA (43) median (IQ <sup>a</sup> )	WithoutRA (27) median (IQ <sup>a</sup> )	<i>P</i>
Pain domains assessed by MPQ <sup>b</sup>			
Sensory (0-40) <sup>c</sup>	23 (18.25-26)	12 (0-19)	0.0001
Affective(0-14) <sup>c</sup>	8 (5-11)	2 (0-6)	<0.0001
Evaluative (0-5) <sup>c</sup>	3 (2-4)	2 (0-2)	0.0006
Miscellaneous (0-17) <sup>c</sup>	8 (6-13)	5 (0-7.5)	0.0015
Total score ofMPQ <sup>b</sup> (0-78) <sup>c</sup>	40 (33-51)	25 (0-32.5)	0.0001

<sup>a</sup>Interquartile range. <sup>b</sup>McGill Pain Questionnaire. <sup>c</sup>Possible range of scores in each domain and in the total MPQ score.

The association between RA and depression and paid work became insignificant when adjusted for the presence of pain. The association with RA and former smoking remained significant (Table 4).

**Table 4.** Univariate logistic regression adjusted for the presence of joint pain of the variables associated with Rheumatoid Arthritis.

Variables	OR <sup>a</sup>	95% CI <sup>b</sup>	<i>P</i>	Adjusted for the presence of joint pain		
				OR <sup>a</sup>	95%CI <sup>b</sup>	<i>P</i>
Workingfor pay	0.31	0.13-0.73	0.007	0.42	0.17-1.05	0.06
Formersmokers	3.91	1.37-11.13	0.011	4.22	1.30-13.69	0.016
Depression	3.7	1.10-12.53	0.03	2.5	0.70-9.14	0.16

<sup>a</sup>Odds ratio. <sup>b</sup>95% Confidence Interval.

There was a significant correlation between anxiety levels and pain intensity by numerical scale, with the total MPQ score with the RADAI and with the HAQ. As well as there was a positive moderate correlation between the anxiety score and all MPQ domains, except the sensory one (Table 5).

**Table 5.** Correlation between anxiety and pain levels, disease activity and physical dysfunction in patients with rheumatoid arthritis.

Variables	rho	<i>P</i>
Levelofpain	0.37	0.014
Pain domains assessed by MPQ <sup>a</sup>	Sensory	0.22
	Affective	0.50
	Evaluative	0.48
	Miscellaneous	0.46
Total score of MPQ <sup>a</sup>	0.38	0.008
RADAI <sup>b</sup>	0.49	0.0006
HAQ <sup>c</sup>	0.38	0.009

<sup>a</sup>McGill Pain Questionnaire. <sup>b</sup>Rheumatoid Arthritis Disease Activity Index. <sup>c</sup>Health Assessment Questionnaire.

The twelve patients with RA and depression and the 34 without depression had a mean age of 54.10 (3.9) and 55.88 (7.5) years, respectively,  $p=0.22$ . We also observed that the two groups did not differ statistically in relation to the proportion between genders (100% vs. 82.35% females,  $p=0.31$ ), schooling  $\geq 12$  years (41.67% vs. 29.41%,  $p=0.48$ ), paid work (25% vs. 38.56%,  $p=0.68$ ), unemployment (36.36% vs. 26.47%,  $p=0.70$ ) and retirement (22.27% vs. 23.53%,  $p=1.0$ ). However, fewer patients with RA and depression were married or in a stable union than patients with RA and without depression (33.33% vs. 76.47%,  $p=0.016$ ),  $OR=0.185$ ,  $95\%CI=0.04-0.76$ ,  $p=0.02$ . The median of pain intensity was significantly higher in the RA group with depression than without depression, as well as the median of MPQ affective domain scores. They also had higher score in evaluative and miscellaneous domains with a trend towards statistical significance. However, there was no statistical difference between the two groups in the medians of the sensory and in the total MPQ score. Mean values of RADAI and HAQ were significantly higher in the RA group with depression than without depression (Table 6).

**Table 6.** Comparison between patients with Rheumatoid Arthritis (RA) with and without depression using the Hospital Anxiety and Depression Scale.

Variables		RA with depression (HADS <sup>a</sup> $\geq 11$ ) (12)	RA without depression (HADS <sup>a</sup> $< 11$ ) (34)	P
		median (IQ <sup>b</sup> )	median (IQ <sup>b</sup> )	
Pain domains assessed by MPQ <sup>c</sup>	Level of pain	8 (7-9)	5 (3.25-7)	0.002
	Sensory (0-40) <sup>d</sup>	22.50 (17.50-26.25)	21.50 (14.25-26)	0.72
	Affective (0-14) <sup>d</sup>	10 (8-12)	7 (4.25-8.75)	0.03
	Evaluative (0-5) <sup>d</sup>	3.50 (2.75-5)	2 (1-3)	0.06
	Miscellaneous (0-17) <sup>d</sup>	11.50 (7-13.25)	6 (5-10)	0.06
Total score of MPQ <sup>c</sup> (0-78) <sup>d</sup>		43.50 (38-55.5)	36.50 (21-44)	0.22
		mean (dp <sup>e</sup> )	mean (dp <sup>e</sup> )	
Time of illness		13.25 (7.11)	16.85 (7.92)	0.17
RADAI <sup>f</sup>		6.38 (1.60)	3.85 (2.28)	0.001
HAQ <sup>g</sup>		1.46 (0.72)	0.91 (0.74)	0.03

<sup>a</sup>Hospital Anxiety and Depression Scale. <sup>b</sup>Interquartile range. <sup>c</sup>McGill Pain Questionnaire. <sup>d</sup>Possible range of scores in each domain and in the total score of MPQ. <sup>e</sup>Standard deviation. <sup>f</sup>Rheumatoid Arthritis Disease Activity Index. <sup>g</sup>Health Assessment Questionnaire.

## Discussion

Our study showed that patients with RA undergoing treatment had a greater chance of depression than patients without RA, but that this association became non-significant after adjusting for the presence of pain. A study evaluated depression using the International Statistical Classification of Diseases (ICD) and showed a higher prevalence of depression in patients with RA (80%) than in people without RA (8%), but no control was performed for the presence of pain (Hassan, Nasr, Mohamed, Kamal, & Elmoghazy, 2019). The prevalence shown in this study was lower in both groups using the HADS. In this sense, it has been observed that the prevalence of depression and anxiety in RA varies during the course of the disease and according to the instrument used to diagnose these psychiatric comorbidities (Matcham, Rayner, Steer, & Hotopf, 2013). However, the prevalence of depression observed in this study, 26.09% in patients with RA, was higher than the 14.8% (95% CI=12-18) described in the meta-analysis by Matcham et al. (2013), when using the HADS. This difference may be because this research was carried out during the COVID-19 pandemic, as patients with RA were under greater stress than people without RA due to the possibility of not having access to medical care (Bhatia & Gupta, 2021).

The prevalence of anxiety of 19.6% described in this study was higher than the 18.6% reported by Covic et al. (2012), also using the HADS. Watad et al. (2017) described that the diagnosis of anxiety using the ICD-9 was significantly higher in 11,782 patients with RA (7.1%) than in 57,973 people without RA (6.1%),  $p=0.001$ . In this study, the prevalence of anxiety in the RA group (19.6%) was higher than in the non-RA group (13%), but the difference was not significant, probably due to the small sample size. However, median anxiety scores were significantly higher in the RA group than in the non-RA group.

The prevalence of joint pain in patients in the RA group undergoing DMARD treatment continued to be significantly higher than in people in the non-RA group, confirming previous observations that pain often persists in these patients even on treatment (Taylor et al., 2010; McWilliams & Walsh 2016; Vergne-Salles et al., 2020). One study showed that 75% European patients and 82% North American patients with RA

undergoing treatment reported moderate to severe pain (Taylor et al., 2010). The prevalence of persistent pain in our RA patients on DMARD treatment was higher, 93.4%, probably due to the inclusion of patients with mild pain.

In our study, the pain intensity assessed by numerical scale and by the MPQ in all domains and in the total score was significantly higher in people in the RA group than in the non-RA group who also reported joint pain. In a British study, mean pain scores in RA patients were two standard deviations at baseline and one standard deviation after one year of treatment, higher than mean values for the general population (McWilliams & Walsh, 2016).

The association with the presence of joint pain in RA patients was attenuated, but remained significant when adjusted for the presence of depression in this study. Thus, other causes that were not evaluated in this study could be contributing to the persistence of pain in the RA group, such as inflammation, central sensitization to pain and the presence of osteoarticular comorbidity, such as osteoarthritis (McWilliams & Walsh, 2016).

Of the factors that were significantly associated with RA in the univariate analysis, only smoking remained significant after adjusting for the presence of pain. In this sense, a history of smoking was associated with more severe pain at the beginning of early RA treatment (OR=1.90, 95% CI=1.17-3.08,  $p=0.009$ ), but was not a predictor of lower pain response after one year of DMARD treatment (OR=0.99, 95% CI=0.49-2.06,  $p=0.99$ ) (McWilliams et al., 2012).

Patients in the RA group were less likely to be working for pay than those in the non-RA group, but this association was attenuated when adjusted for the presence of pain. In this sense, pain in patients with RA has been shown to be an independent predictor of work difficulty [adjusted hazard ratio (HR)=2.45, 95% CI=1.02-1.61,  $p=0.001$ ] (McWilliams, Varughese, Young, Kiely, & Walsh, 2014). Studies have shown that, despite the reduction of this problem in recent decades, RA continues to be a factor associated with prolonged absences from work due to illness, in addition to the fact that these patients continue to have a lower chance of returning to work after long periods of absence due to illness or unemployment (Hansen et al., 2016).

The association of depression with RA also became non-significant when adjusted for the presence of pain. In people without depression, increased levels of pain were predictor of the incidence of depression even after adjusting for sociodemographic characteristics, lifestyle, physical dysfunction and chronic illness (HR=1.08, 95% CI=1.01-1.18,  $p=0.034$ ), but depression was not an independent predictor of pain incidence (Hilderink et al., 2012).

However, patients with RA and depression had medians of pain intensity by numerical scale significantly higher than patients with RA and without depression, confirming a previous study in which patients with RA undergoing treatment for depression reported more severe pain than moderate or mild pain than patients without depression (Taylor et al., 2010).

We also confirmed the studies that showed the association of depression and anxiety with physical dysfunction (Jamshidi et al., 2020; Uda et al., 2021), being described that the association of moderate to severe depression with physical dysfunction is independent of disease activity (Isnardi et al., 2021).

Patients with RA and depression had significantly higher disease activity when assessed by the RADAI than patients with RA and without depression, but it must be noted that this instrument does not include laboratory assessment of inflammation, such as ESR or CRP. In women with RA, an association of depression with all components of the *Clinical Disease Activity Index* was observed, which also does not include laboratory markers of inflammation (Sautner, Puchner, Akin, & Pieringer, 2020). However, some authors have not demonstrated an association between depression and disease activity when assessed using the DAS-28 (Jamshidi et al., 2016; Juárez-Rojop et al., 2020; Uda et al., 2021). Others showed a significant association of depression only with subjective components of the DAS-28, such as the number of painful joints and global health assessment, both in cross-sectional studies (Michelsen et al., 2017) and after one year of treatment (Boer, Huizinga, & van der Helm-van Mil, 2019).

There was a positive and significant correlation between anxiety levels and RADAI, reinforcing the findings of a Mexican study that showed an association between high DAS-28 scores and anxiety (Juárez-Rojop et al., 2020). Nevertheless, another recent study showed no association between the total DAS-28 score and anxiety symptoms, observing only an association between anxiety and depression and the patients' global health assessment (Uda et al., 2021).

Although it was observed that pain as a stressor decreased with advances in disease treatment, new stressors, which are associated with the presence of depression and anxiety, such as family and work, worsened even with the improvement of RA disease activity (Otake et al., 2013).

In this sense, patients with RA and depression were less likely to be married or in a stable union than patients with RA and without depression. Our results are partially in line with a study that demonstrated that unmarried RA patients had significantly more psychological problems and higher levels of affective pain assessed by the MPQ than married patients in a non-stressful relationship, but did not differ from those married in a stressful relationship (Reese, Somers, Keefe, Mosley-Williams, & Lumley, 2010).

In this study, there was a significant correlation between anxiety levels of patients with RA and all pain domains, except the sensory one, assessed by the MPQ. Patients with RA and depression had significantly higher median scores in the affective component and a trend towards significance in the evaluative and miscellaneous pain domains compared to patients with RA and without depression, but there was no difference in the sensory domain and also the total score of the MPQ between these two groups. It was described that anxiety and depression were both related to current and next week pain, nevertheless it was observed that the direct effect of anxiety is twice as large as that of depression on pain perception in women with RA, and when anxiety is controlled, the effect of depression is reduced (Smith & Zautra, 2008). Although, patients with RA used a greater number of emotional than sensory qualifiers to describe pain, both the affective and sensory components are significantly higher in patients with DAS28 > 3.2 (Vergne-Salle et al., 2020).

These differences in the qualitative assessment of pain suggest the need for a better understanding of the pain experience in patients with RA and the need for new forms of pain assessment and the diagnosis of psychiatric comorbidities in the clinical follow-up of these patients, so that this symptom can be properly treated.

Limitations of this study include convenience sampling, small number of participants, and inclusion of RA patients with heterogeneous disease duration and DMARD treatment. Due to the implementation of social isolation, we were unable to assess disease activity, the presence of neuropathic pain, and pain sensitization through instruments that required physical and/or laboratory examinations.

## Conclusion

In conclusion, pain persisted in RA patients undergoing treatment with conventional and/or biological DMARD. Patients with RA and depression do not differ in the sensory component of pain compared to patients with RA, without depression. The level of anxiety, on the other hand, correlates with all pain domains, except for the sensory component. Further studies are required to verify whether a qualitative assessment of pain could complement the information obtained through physical examination and from composite indices of disease activity that could better direct the treatment of pain reported by patients with RA.

## Acknowledgements

We would like to thank the funding provided by the Institutional Program for High School Scientific Initiation Scholarships (PIBIC-EM) of the National Council for Scientific and Technological Development (CNPq), made available by the Grande Dourados Federal University and intended for the authors of the study. We are also grateful to collaborators Aline Pires Pinto, Amanda Paula Costa, Jamilli Monteiro Sampaio, Maria Tereza Martins Greef and Sara Barbosa Cardoso for their participation and contribution in obtaining data.

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