EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2017.16100

Original Article

Rheumatoid Arthritis: Are psychological factors effective in disease flare?

Volkan Yılmaz, Ebru Umay, İbrahim Gündoğdu, Zeliha Özgür Karaahmet, Arif Erhan Öztürk

Abstract

Objective: Rheumatoid arthritis (RA) is clinically an undulant disease, and reasons for flare or remission vary. We aimed to identify factors potentially associated with disease flare and remission.

Material and Methods: Two hundred and seventy-four patients with RA who were admitted to our center between January 2010 and January 2016 were included. Disease activity was evaluated using disease activity score 28 (DAS 28); functional status was evaluated using the modified Health Assessment Questionnaire (m-HAQ), a questionnaire that comprises flare or remission domains such as psychological stress and mood status, physical trauma, nutrition regimen, infection, antibiotic use, and seasonal weather changes. Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) were used to identify if patients had a mood disorder. Four subscales of Arthritis Impact Measurement Scale-2 (AIMS-2) (level of tension, mood, general perception of health, and satisfaction with health) were used to determine patient quality of life.

Results: Of the 274 patients, 261 were female (95.3%) and 13 were male (4.7%); the mean age was 52.10±9.41 years. According to patients' perception, the most frequent reasons for joint symptoms were psychological stress/mood disorder (86.1%), followed by infection (49.6%) and trauma (46.4%). The most frequent factors for remission of symptoms were antibiotic use (42.7%), cold weather (34.3%), and hot weather (19%).

Conclusion: Psychological stress and mood status are independent factors for relapse periods in patients with RA. These should be considered particularly in patients who are resistant to different treatment regimens and in whom any other reason for disease flare is not obvious.

Keywords: Depression, anxiety, rheumatoid arthritis, disease flare

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease with an undulant course and has a prevalence of 0.2%-1.2% (1). Disease remission and flare periods may be associated with different factors. Psychological stress and mood disorders such as depression and anxiety are more frequent in patients with RA. A recent meta-analysis reported 14.8% prevalence of depression (2), while the estimated prevalence in general population is 5% (3). In another study, the prevalence of anxiety in patients with RA was reported to be 25.1% (4). Anxiety concomitant with depression is reportedly observed in 16.3% of patients with RA (5). High levels of distress are also common. In a previous study, high levels of persistent distress were reported in 12% of RA patients in the first 10 years after the first diagnosis (6). The relationship between mood disorders and RA seems bidirectional. Depression and anxiety are associated with flare periods, resulting with pain and fatigue (7, 8). Joint pain and tenderness are more frequent in patients with concomitant mood disorders (9). These factors may influence the health behavior of patients, such as medication adherence and smoking, which results with poorer patient outcome and increased mortality risk (10-12).

Although a relationship exists between mood disorders and RA, the underlying mechanisms remain unclear. Depression and anxiety is associated with immune and neurotransmitter dysregulation (13). This dysregulation may lead to the activation of autoimmune mechanisms that play a central role in RA. Further, altered pain and reduction of physical activity may decrease endorphin levels, causing increased pain sensation and patient discomfort, thereby resulting with depression (14). Chronic pain syndromes such as RA and depression have common pathways, and a dysfunction of these pathways may cause a cycle of pain and depression. Further molecular studies of these pathways are thus required.

Pain perception depends on different factors in patients with RA. Recent studies have reported differences related with gender, age, and sociodemographic parameters such as socioeconomic status and education level. Fillingim et al. (15) reported that women with RA have more severe pain with a greater frequency and duration than men, with respect to sociodemographics. A recent meta-analysis including 27 studies on RA report-

Physical Medicine and Rehabilitation Clinic, Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey

Address for Correspondence: Volkan Yılmaz, Physical Medicine and Rehabilitation Clinic, Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey

E-mail: dryilmazv@hotmail.com

Submitted: 13 November 2016
Accepted: 5 March 2017

ed increased pain perception in females than in men with RA (16). Jakobsson et al. (17) reported a positive linear relationship between age and pain perception in patients with RA. Moreover, a recent study reported increased pain perception in patients with RA who have formal education of <12 years (7). Massardo et al. (18) reported more severe pain in patients with early RA who have low socioeconomic status. Another longitudinal study in women confirmed this result, witnessing a higher level of pain in patients with greater financial worries (19).

Consideration of psychological distress and mood disorders in patients with RA is overlooked. Particularly in patients with unexpected relapse periods or treatment resistance, this issue is not recognized (20). Although data on this comorbidity are present, data pertaining to the effect of mood disorders on aggravation or remission periods of the disease are still insufficient. We aimed to evaluate the association between disease activity and comorbid mood disorders.

Material and Methods

Study design

Two hundred and seventy-four patients with a diagnosis of RA, according to the criteria of American Rheumatism Association (ACR), who attended outpatient clinics for follow-up visits between January 2010 and January 2016 were included in this study. The study was approved by the ethics committee of the hospital, and signed informed consents were obtained from patients.

Patients with a diagnosis of chronic RA (at least 1 year of disease duration) and aged between 40 and 75 years were included. Exclusion criteria were as follows: age under 40 years and over 75 years, trauma and/or history of an operation, diabetes mellitus, acute and/or chronic liver and kidney disease, severe heart failure, thyroid diseases, amyloidosis, malignancy, vitamin B12 deficiency, additional connective tissue disease such as Sjögren's syndrome and/or vasculitis symptoms, previously diagnosed peripheral nervous system involvement, and positive pathological reflexes.

Demographic features of patients including age, gender, education level, marital status, and hand dominancy and disease features including diagnosis time, duration of morning stiffness, number of tender and swollen joints, and general perception of health were recorded. Biochemical parameters such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were also recorded. Disease activity was assessed using disease activity score 28 (DAS 28).

Assessments

Functional limitations of patients according to the modified Health Assessment Questionnaire (m-HAQ) were assessed. This 10-item questionnaire is used to measure disability or physical function in patients with rheumatic diseases, and patients are considered from 0 (minimal loss of function) to 3 (completely disabled) for every question over 60 points in total. Mood status was evaluated using Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI). BDI and BAI are both 21-questioned multiple-choice self-report inventories and are widely used in psychometric tests for measuring the severity of depression and anxiety. For depression, 17 points and over are significant; for anxiety, 10 points and over are significant. Patient quality of life was assessed using the four subscales of Arthritis Impact Measurement Scale-2 (AIMS-2): level of tension, mood status, satisfaction with health, and general perception of health. Questions for each subscale were individually scored from 1 to 5 (0-10 points). Higher scores indicated worse quality of life. Patients were also evaluated using a questionnaire that included flare or remission domains; common factors for aggravation and remission were recorded.

Comparisons

Patients were compared according to the presence of the three most frequent factors associated with disease flare or remission, disease severity, functional disability, anxiety, depression, and quality of life.

Table 1. Demographic features of patients

Parameters	n=274 ave±SD, n (%)
Age (year)	52.10±9.41
Marital status	
Married	219 (79.9)
Single	12 (4.4)
Divorced	8 (2.9)
Widow	35 (12.8)
Educational status	
Illiterate	69 (25.2)
Just literate	36 (13.1)
Primary school graduates	130 (47.4)
Secondary school graduates	18 (6.6)
High school graduates	19 (6.9)
College/university graduates	2 (0.7)
Dominant hand	
Right	264 (96.4)
Left	10 (3.6)

ave±SD: average±standard deviation

Statistical analysis

Data analysis was performed using Statistical Package for the Social Sciences (IBM Corp.; Armonk, NY, USA) 22.0 for Windows. Continuous variables were evaluated using the Kolmogorov-Smirnov test for whether or not they were different from normal distribution. Descriptive statistics are reported as mean±standard deviation for continuous variables and frequencies and percentages (%) for nominal variables using chi-square test. Significance of the differences between the groups was investigated using the Mann-Whitney U test. Logistic regression analysis was used to determine significant correlation. P<0.05 indicated statistical significance.

Results

Of total, 261 patients were female (95.3%) and 13 were male (4.7%); the mean age was 52.1±9.41 years. The demographic features of patients are shown in Table 1, and the disease characteristics and functional status are presented in Table 2.

Table 2. Disease characteristics and functional status of patients

Parameters	n=274 ave±SD, n (%)
Disease time (year)	13.31±9.32
Diagnosis time (year)	5.87±2.41
Morning stiffness (min)	47.84±21.43
DAS 28 score	4.42±1.18
Number of tender joints	8.64±6.18
Number of swollen joints	2.24±1.25
ESR level (mm/h) (0-20)	27.43±18.30
VAS (0-100 mm)	44.27±24.13
CRP (µg/dL) (0-5)	13.08±12.61
RF (IU/mL) (0-20)	98.22±56.64
m-HAQ (0-3)	1.21±0.68
BDI score (0-63)	21.06±11.89
BAI score (0-63)	20.01±11.92
Level of tension (AIMS-2) (0-10)	5.50±1.74
Mood status (AIMS-2) (0-10)	5.49±1.58
Satisfaction with health (AIMS-2) (0-10)	7.32±2.85
General perception of health (AIMS-2) (0-10)	7.29±1.94

ave±SD:average±standard deviation; DAS 28: Disease Activity Score 28; ESR: Erythrocyte Sedimentation Rate; VAS: Visual Analog Scale; CRP: C-reactive protein; RF: rheumatoid factor; m-HAQ: Modified Health Assessment Questionnaire; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; AIMS-2: Arthritis Impact Measurement Scale-2

Table 3. Factors associated with disease flare, according to patient perception

Related Factor	n=274, n (%)
Psychological distress, mood disorder	236 (86.1)
Physical trauma	127 (46.4)
Nutrition	48 (17.5)
Animal based	
Red Meat	24 (50)
White Meat	0
Milk and milk products	0
Vegetarian diet	1 (2.1)
Frozen food	0
Fast-food diet	4 (8.3)
Spicy food	5 (10.4)
Floury food	8 (10.3)
Sweet food	6 (12.5)
Infection	136 (49.6)
Smoking	32 (11.7)
Hot weather	98 (35.8)
Cold weather	56 (20.4)
Seasonal changes	19 (6.9)
Fatigue	42 (15.3)
Prolonged standing or immobility	18 (6.6)

Table 4. Factors associated with disease remission, according to patient perception

Related Factor	N (%)
Antibiotic use	117 (42.7)
Nutrition	
Animal based	29 (10.6)
Red meat	0
White meat	4 (13.8)
Milk and milk products	5 (17.22)
Vegetarian diet	20 (69.0)
Frozen food	0
Fast food diet	0
Spicy food	0
Floury food	0
Sweet food	0
Cold weather	94 (34.3)
Hot weather	52 (19.0)

Table 5. Relationship between factors associated with disease flare and functional disability, disease activity, anxiety, and depression levels

Parameters	Stress (+) n=236 ave±SD	Stress (-) n=38 ave±SD	Trauma (+) n=127 ave±SD	Trauma (-) n=147 ave±SD	Infection (+) n=136 ave±SD	Infection (-) n=138 ave±SD
m-HAQ	1.09±0.76	1.11±0.65	1.07±0.63	1.06±0.68	1.09±0.65	1.04±0.66
DAS-28	4.60±1.49*	4.01±1.24	4.68±1.58	4.41±1.43	4.63±1.48	4.06±1.55*
BDI	22.72±11.01*	15.33±7.08	23.80±11.55*	16.30±9.97	23.55±10.65*	17.48±10.99
BAI	20.22±12.03*	10.75±8.13	23.51±13.05	15.22±10.56	23.96±12.48	17.68±11.37

ave±SD: average±standard deviation; DAS 28: Disease Activity Score 28; m-HAQ: modified Health Assessment Questionnaire; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory

Table 6. Relationship between factors associated with disease remission and functional disability, disease activity, anxiety, and depression levels

Parameters	Antibiotic use (+) n=117 ave±SD	Antibiotic use (-) n=157 ave±SD	Cold weather (+) n=94 ave±SD	Cold weather (-) n=180 ave±SD	Hot weather (+) n=52 ave±SD	Hot weather (-) n=222 ave±SD
m-HAQ	1.24±0.62*	1.01±0.67	1.11±0.53	1.12±0.57	1.06±0.54	1.12±0.66
DAS-28	4.56±1.59	4.53±1.41	4.62±1.61	4.53±1.50	3.62±1.37*	4.60±1.51
BDI	22.77±10.32	21.46±11.35	22.93±11.81	21.92±10.80	22.06±14.79	22.04±10.64
BAI	20.72±12.58	18.26±11.51	21.19±14.10	19.10±11.74	17.25±11.21	19.49±12.09

ave±SD: average±standard deviation; DAS 28: Disease Activity Score 28; m-HAQ: modified Health Assessment Questionnaire; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory

Most patients had at least 5 years of formal education (n=130, 47.4%) and almost all patients were right-handed (n=264, 96.4%). The average duration of the disease was 13.31±9.32 years, while the average time of diagnosis was 5.87±2.41 years. Average disease activity score was compatible with high disease activity (4.42±1.18), and average m-HAQ score was associated with moderate disability (1.21±0.68). Average BDI and BAI scores were related with the presence of anxiety and depression (21.06±11.89 and 20.01±11.92, respectively). The level of tension and mood status subscales of AIMS-2 were compatible with a mild deterioration in patient quality of life (5.50±1.74, 5.49±1.58 respectively), while the satisfaction with health and general perception of health subscales were associated with a severe deterioration (7.32±2.85 and 7.29±1.94, respectively).

Factors associated with disease flare and remission according to patient perception are show in Tables 3, 4.

Two hundred and sixty-one patients (98.8%) reported at least one factor for disease flare, while 144 (54.4%) reported at least one factor for disease remission. According to patient perception, the most frequent reasons for joint symptoms were psychological stress and mood disorder (86.1%), followed by infection (49.6%) and trauma (46.4%). The most frequent factor for remission of symptoms was antibiotic use (42.7%), cold weather (34.3%), and hot weather (19.0%).

The relationship between factors associated with disease flare or remission and functional disability (m-HAQ), disease activity (DAS-28), and anxiety and depression levels (BAI and BDI) is presented in Tables 5, 6.

Patients who reported psychological distress and infection as aggravation factors for symptoms had more severe disease activity (p=0.043 and 0.047, respectively). Patients who reported antibiotic use as the remission factor for symptoms had more functional disability (p=0.005), while those who reported hot weather as the factor had lower disease activity (p=0.015).

Patients who reported psychological distress, trauma, and infection as aggravation factors had significantly higher depression (p=0.005, 0.004, and 0.028, respectively) and anxiety (p=0.004, 0.010, and 0.023, respectively) levels.

In regression analysis, psychological distress was the most common factor for increased disease activity (p=0.043), while hot weather

Table 7. Relationship between factors associated with disease flare and AIMS-2 subscales

AIMS-2 subscales	Stress (+) n=236 ave±SD	Stress (-) n=38 ave±SD	Trauma (+) n=127 ave±SD	Trauma (-) n=147 ave±SD	Infection (+) n=136 ave±SD	Infection (-) n=138 ave±SD
Level of tension	5.63 1.28	5.17 1.88	5.64±1.82*	4.93±2.05	5.60±1.74	5.19±1.92
Mood status	5.48±1.63*	4.56±1.89	5.58±1.65	5.20±1.69	5.57±1.66	5.20±1.68
Satisfaction with health	7.31±2.99	6.31±2.33	7.41±2.01	7.03±3.65	7.50±3.47	6.93±2.26
General perception of health	7.48±2.01*	6.15±2.38	7.56±1.88*	6.82±2.14	7.46±1.96*	6.91±2.09

ave±SD:average±standard deviation; AIMS-2: Arthritis Impact Measurement Scale 2; *statistically significant (p<0.005)

Table 8. Relationship between factors associated with disease remission and AIMS-2 subscales

AIMS-2 subscales	Antibiotic (+) n=117 ave±SD	Antibiotic (-) n=157 ave±SD	Cold weather (+) n=94 ave±SD	Cold weather (-) n=180 ave±SD	Hot weather (+) n=52 ave±SD	Hot weather (-) n=222 ave±SD
Level of tension	5.34±1.78	5.44±1.79	5.50±1.75	5.38±1.86	4.90±2.09	5.23±1.82
Mood status	5.50±1.63	5.31±1.71	5.49±1.59	5.38±1.69	6.15±1.92	5.94±1.65
Satisfaction with health	7.46±3.63	7.12±2.25	7.48±2.08	7.18±3.05	7.29±1.97	7.21±3.01
General perception of health	7.32±1.75	7.18±2.24	7.33±1.70	7.14±2.08	7.22±1.66	7.14±2.06

ave±SD: average±standard deviation; AIMS-2: Arthritis Impact Measurement Scale 2

was the most common factor for decreased disease activity (p=0.018). Antibiotic use was found to be an improving factor for functional disability (p=0.005). Presence of psychological distress, physical trauma, and infection were significantly associated with anxiety (p=0.001, 0.004, and 0.028, respectively) and depression (p=0.001, 0.009, and 0.023, respectively).

The relationship between factors associated with disease flare and remission and AIMS-2 subscales are given in Tables 7, 8.

Depressive mood was significantly higher in patients who reported psychological distress as an aggravating factor (p=0.030), while level of tension was significantly higher in those who reported physical trauma (p=0.033). General perception of health scores were significantly high in patients who reported psychological distress, physical trauma, and infection (p=0.035, 0.004, and 0.029, respectively). None of the disease remission factors (antibiotic use, cold weather, and hot weather) were significantly related with AIMS-2 subscales (p>0.05). In regression analysis, psychological distress was found as an effective factor on mood status (p=0.011), while physical trauma was effective on level of tension (p=0.013). Psychological distress, physical trauma, and infection were effective factors on general perception of health (p=0.013, 0.004, and 0.029, respectively).

Discussion

We found that most common factors for disease flare in patients with RA were psychological stress/mood disorder (86.1%), infection (49.6%), and trauma (46.4%). The most frequent factors for remission of symptoms were antibiotic use (42.7%), cold weather (34.3%), and hot weather (19%). Further, we found that common factors responsible for RA aggravation were also related with increased functional disability and decreased quality of life. Psychological stress was significantly associated with higher disease activity, while hot weather was associated with lower disease activity. Antibiotic use was an effective factor for better functional status. Psychological stress was negatively correlated with mood status, while physical trauma was positively correlated with level of tension from a patient quality of life perspective. Psychological stress, physical trauma, and infection were associated with depressive mood and lower quality of life.

Rheumatoid arthritis is a relapsing and remitting disease, and factors that are responsible for its aggravation or remission periods vary. Different sociodemographic factors such as gender (16), age (17), socioeconomic status (18), and education level (7), physical trauma, seasonal changes, and infection are attributed to aggravation periods of RA. In this study, the average patient age was 52.10±9.41 years, and 85.7% patients had 5 years of formal education or less. Moreover, psychological stress and mood disorder (86.1%) were the most common relapsing reasons, followed by infection (49.6%) and trauma (19%). Mood disorders such as depression and anxiety are known risk factors for aggravation of the disease, both independently and in association with other provoking factors. Depression and anxiety not only aggravate RA but also increase pain perception (21). However, the relationship between pain and depression is bidirectional. Pain and fatigue seem to be the best predictors of depression in patients with RA (22). Similar to recent data, in our study, we found significantly higher disease activity in patients who reported psychological distress or infection as the relapsing factor, and we found significantly lower disease activity in those who reported hot weather as the remission factor. Also, we found anxiety and depression to be more common in patients who reported psychological distress and infection as relapsing factors. According to the AIMS-2 subscales, we noted that psychological trauma is related with depressive mood and physical trauma is related with high levels of tension as relapsing factors. In addition to psychological stress and physical trauma, infection is related with lower satisfaction with health and worse perception of health.

The relationship between chronic pain syndromes such as RA and mood disorders such as depression and anxiety can be explained through different mechanisms. These disorders can increase pain perception via several biological pathways (23). Hypothalamic pituitary adrenal (HPA) axis dysregulation accompanied with corticotropin-releasing hormone respon-

siveness, resulting with depression and fatigue, may be one of such mechanisms (24). Proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin 1 (IL-1), and interleukin 6 (IL-6) may cause cartilage destruction, resulting with pain and HPA axis dysregulation at the same time (25). Besides biological pathways, cognitive mechanisms are also associated with pain perception in patients with RA. Catastrophizing may enhance pain ratings in patients with chronic pain syndromes (26). Perception of pain and other symptoms may change because of hypervigilance, misinterpretation, and misattribution, as well as somatization (27, 28). High levels of anxiety are a predictor for pain perception and pain behavior, and are common in patients with RA (29). In the present study, four subscales of AIMS-2 were used, and both depression and anxiety were related with increased pain perception and level of tension, decreased satisfaction with health, and general perception of health; these data are similar with those of recent studies. In a recent study, anxiety was found to be a better predictor for pain than depression (30).

Chronic pain syndromes may present with different clinical features and may be a part of chronic arthritis. Although clinical appearances vary, most involve same biological pathways, which are common with mood disorders, such as anxiety and depression, including neurotransmitter pathways. Hence, perception of pain and mood disorders may correspondingly interact, and it is generally difficult to determine whether psychological stress is a predisposing factor for disease flare or a consequence of the disease.

There is growing evidence about the relationship between pain perception and behavior of patients with RA and mood disorders. This relationship is an important issue for evaluating patients. Patients with pain due to RA should be considered not only from a clinical perspective but also from an affective aspect of pain. Management of psychological symptoms in such patients should be multidisciplinary and should include psychoeducational programs.

Another aggravation factor for disease activation is infection in RA patients, which may increase pain due to anxiety and depression and worse quality of life. We found a significant relationship between the presence of infection, depressive mood, and lower quality of life, which is in agreement with recent data. Serum ESR and CRP levels may alter with infections and interfere with other reasons of disease activation. Antibiotic use may be beneficial to identify the infectious factors of disease activation. In our study, we did not find any relationship between antibiotic use, depression, anxiety, and quality of life. This may be due to long disease duration. However, antibiotic use has been reported to be an effective factor for recovery of functional disability, possibly due to the treatment of potential infections that may be associated with disease activation.

Physical trauma is generally related with an overuse of affected joints in patients with RA. We found a significant relationship between trauma, mood disorders (both depression and anxiety), and quality of life in our study, as expected due to increased pain sensation. In addition, we found a significant relationship between level of tension and physical trauma. This relation is possibly associated with high levels of depression and anxiety. However, degenerative changes of osteoarthritis are common morbidities in patients with RA. Interestingly, this comorbidity may clarify the severe joint pain in patients with a low disease activity. Compatible with this finding, we found hot weather as a remission factor, probably due to the suppression of osteoarthritic symptoms.

Disease activity is associated with several factors in patients with RA. Physical and psychological trauma and infections are the most common factors for disease aggravation. In elderly, joint symptoms of RA concomitant mood disorders may present with lower disease activity due to osteoarthritic changes. Hence, these patients should be considered for osteoarthritic changes as well as periarthritic changes of RA.

To conclude, psychological stress and mood status are independent factors for relapse periods in patients with RA. These factors should be considered, particularly in patients who are resistant to different treatment regimens and in whom any other reason for disease flare is not obvious.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara Dışkapı Training and Research Hospital, Ankara, Turkey (2008/13/7).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - V.Y., E.U.; Design - V.Y., E.U.; Supervision - V.Y., I.G.; Resources - V.Y., Z.K.; Materials - V.Y., A.O.; Data Collection and/or Processing - E.U., I.G.; Analysis and/or Interpretation - V.Y., Z.K.; Literature Search - V.Y., A.O.; Writing Manuscript - V.Y., E.U.; Critical Review - V.Y., I.G.; Other - A.O., I.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Alamos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis based on the 1987 American Collage of Rheumatology criteria: a systematic review. Sem Arthritis Rheum 2006; 36: 182-8. [CrossRef]
2. Matcham F, Rayner L, Steer S, Hotopf M. The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. Rheumatology (Oxford) 2013; 52: 2136-48. [CrossRef]
3. Waraich P, Goldner EM, Somers JM, Hsu L. Prevalence and incidence studies of mood disorders: a systematic review of the literature. Can J Psychiatry 2004; 49: 124-38. [CrossRef]
4. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006; 166: 1092-7. [CrossRef]
5. Rayner L, Matcham F, Hutton J, Stringer C, Dobson J, Steer S, et al. Embedding integrated mental health assessment and management in general hospital settings: feasibility, acceptability and prevalence of common mental disorder. Gen Hosp Psychiatry 2014; 36: 318-24. [CrossRef]
6. Norton S, Sacker A, Young A, Done J. Distinct psychological distress trajectories in rheumatoid arthritis: findings from an inception cohort. J Psychosom Res 2011; 71: 290-5. [CrossRef]
7. Kojima M, Kojima T, Suzuki S, Oguchi T, Oba M, Tsuchiya H, et al. Depression, inflammation and pain in patients with rheumatoid arthritis. Arthritis Care Res 2009; 61: 1018-24. [CrossRef]
8. Matcham F, Ali S, Hotopf M, Chalder T. Psychological correlates of fatigue in rheumatoid arthritis: A systematic review. Clin Psychol Rev 2015; 39: 16-29. [CrossRef]
9. Baumeister H, Balke K, Harter M. Psychiatric and somatic comorbidities are negatively associated with quality of life in physically ill patients. J Clin Epidemiol 2005; 58: 1090-100. [CrossRef]
10. DiMatteo M, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment:meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med 2000; 160: 2101-7. [CrossRef]
11. Pratt LA, Brody DJ. Depression and smoking in US. household population aged 20 and over, 2005-2008. NCHS Data Brief 2010; 34: 1-8.
12. Ang DC, Choi H, Kroenke K, Wolfe F. Comorbid depression is an independent risk factor for mortality in patients with rheumatoid arthritis. J Rheumatol 2005; 32: 1013-9.
13. Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E, Neels H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. Cytokine 1997; 9: 853-8. [CrossRef]
14. Covic T, Adamson B, Spencer D, Howe G. A biopsychosocial model of pain and depression in

rheumatoid arthritis: a 12-month longtidunal study. Rheumatology (Oxford) 2003; 42: 1287-94. [CrossRef]
15. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley III JL. Sex, gender, and pain: A review of recent clinical and experimental findings. J Pain 2009; 10: 447-85 [CrossRef]
16. Barnabe C, Bessette L, Flanagan C, Leclerlq S, Steiman A, Kalache F, et al. Sex differences in pain scores and localization in inflammatory arthritis: a systematic review and meta-analysis. J Rheumatol 2012; 39: 1221-30. [CrossRef]
17. Jakobsson U, Hallberg IR. Pain and quality of life among older people with rheumatoid arthritis and/or osteoarthritis: a literature review. J Clin Nurs 2002; 11: 430-43. [CrossRef]
18. Massardo L, Pons-Estel BA, Wojdyla D, Cardiel MH, Galarza-Maldonado CM, Sacnun MP, et al. Early rheumatoid arthritis in Latin America: Low socioeconomic status related to high disease activity at baseline. Arthritis Care Res (Hoboken) 2012; 64: 1135-43. [CrossRef]
19. Rios R, Zautra AJ. Socioeconomic disparities in pain: The role of economic hardship and daily financial worry. Health Psychol 2011; 30: 58-66. [CrossRef]
20. Hider SL, Tanveer W, Brownfield A, Mattey DL, Packham JC. Depression in RA patients treated with anti-TNF is common and under-recognized in rheumatology clinic. Rheumatology 2009; 48: 1152-4. [CrossRef]
21. Cheng T, Zhang G. Worldwide research productivity in the field of rheumatology from 1996 to 2010: A bibliometric analysis. Rheumatology (Oxford) 2013; 52: 1630-4. [CrossRef]
22. Wolfe F, Michaud K. Predicting depression in rheumatoid arthritis: The signal importance of pain extent and fatigue, and comorbidity. Arthritis Rheum 2009; 61: 667-73. [CrossRef]
23. Rogers HL, Brotherton HT, De Luis A, Olivera-Plaza SL, Cordoba-Pati-o AF, Pena-Altmar ML. Depressive symptoms are independently associated with pain perception in Colombians with rheumatoid arthritis. Acta Reumatol Port 2015; 40: 40-9.
24. Zautra AJ, Yocum DC, Villanueva I, Smith B, Davis MC, Attrep J, et al. Immune activation and depression in women with rheumatoid arthritis. J Rheumatol 2004; 31: 457-63.
25. Choy E. Understanding the dynamics: Pathways involved in the pathogenesis of rheumatoid arthritis. Rheumatology (Oxford) 2012; 51: v3-v11. [CrossRef]
26. Plata-Mu-oz M, Castillo-Olivares M, Guevara-López U. Evaluación de afrontamiento, depresión, ansiedad e incapacidad funcional en pacientes con dolor crónico. (Assessing coping, depression, anxiety and functional disability in patients with chronic pain.) Rev Mex Anest 2004; 27: 16-23.
27. Dersh J, Polatin PB, Gatchel RJ. Chronic pain and psychopathology: research findings and theoretical considerations. Psychosom Med 2002; 64: 773-86.[CrossRef]
28. Duddu V, Isaac MK, Chaturvedi SK. Somatization, somatosensory amplification, attribution styles and illness behaviour: a review. Int Rev Psychiatry 2006; 18: 25-33. [CrossRef]
29. Covic T, Cumming SR, Pallant JF, Manolios N, Emery P, Conaghan PG, et al. Depression and anxiety in patients with rheumatoid arthritis: Prevalence rates based on a comparison of the Depression, Anxiety and Stress Scale (DASS) and the Hospital, Anxiety and Depression Scale (HADS). BMC Psychiatry 2012; 12: 6. [CrossRef]
30. Ødegård S, Finset A, Mowinckel P , Kvien TK, Uhlig T. Pain and psychological health status over a 10-year period in patients with recent onset rheumatoid arthritis. Ann Rheum Dis 2007; 66: 1195-1201. [CrossRef]