Duazary / Vol. 22 - 2025/ e6759
DOI: https://doi.org/10.21676/2389783X.6759

Review article

Rheumatoid arthritis and major depressive disorder: From shared mechanisms to therapeutic opportunities

Artritis reumatoide y trastorno depresivo mayor: de mecanismos compartidos a oportunidades terapéuticas

Mateo López-Trujillo[1] * Valentina De-Alba-Higuita[2] * Sofía Gutiérrez-Victoria[3]
Daniela Ortiz-Piedrahita[4] * Valeria Vásquez-Estrada[5] * Paola Andrea Serna-Jiménez[6]

Para citar este artículo: López-Trujillo M, De-Alba-Higuita V, Gutiérrez-Victoria S, Ortiz-Piedrahita S, Vásquez-Estrada V, Serna-Jiménez P. Rheumatoid arthritis and major depressive disorder: From shared mechanisms to therapeutic opportunities. Duazary. 2025;22:e6759. https://doi.org/10.21676/2389783X.6759.

Received August 6, 2025
Accepted November 10, 2025
Published online December 19, 2025

ABSTRACT

Rheumatoid arthritis is a chronic, multisystemic, autoimmune inflammatory disease. Mood disorders, such as depression, are common in patients with this disease. Evidence suggests that rheumatoid arthritis and major depressive disorder have a bidirectional association, the explanation for which has not yet been fully elucidated; however, current evidence points to the possibility of an everyday pathophysiological basis. Given the significant impact of these diseases on quality of life and functionality, this topic review was conducted to provide the most up-to-date literature on their relationship and its therapeutic implications. This goal was achieved through a systematic search of PubMed, followed by organization into pathophysiology, impact on quality of life, and joint diagnosis and treatment. The results indicate that depression and rheumatoid arthritis are consistently associated: both diseases appear to increase the likelihood of developing each other and may exacerbate each other. It is concluded that these are two chronic, high-impact diseases with a potentially shared pathophysiological basis that is not yet fully understood, but for which both indications and certainties support definite knowledge.

Keywords: Major depressive disorder; Rheumatoid arthritis; Physiology; Quality of life; Therapeutics.

RESUMEN

La artritis reumatoide es una enfermedad autoinmune inflamatoria crónica y multisistémica. Los trastornos del estado de ánimo, como la depresión, son comunes en pacientes con esta enfermedad. La evidencia sugiere que la artritis reumatoide y el trastorno depresivo mayor presentan una asociación bidireccional cuya explicación aún no ha sido completamente dilucidada; sin embargo, la evidencia actual apunta a una base fisiopatológica común. Basada en que son enfermedades de alto impacto en la calidad de vida y la funcionalidad de las personas, surge esta revisión del tema con el objetivo de proporcionar la literatura más actualizada sobre la relación entre ambas y sus implicaciones terapéuticas. Esto se logró mediante una búsqueda sistemática de información en PubMed y su posterior organización en fisiopatología, impacto en la calidad de vida y diagnóstico y tratamiento conjuntos. Los resultados indican que la depresión y la artritis reumatoide están consistentemente asociadas: aparentemente las dos enfermedades aumentan la posibilidad de padecer la otra y, además, parece ser que se agravan entre sí. Se concluye que son dos enfermedades crónicas y de alto impacto, con una base fisiopatológica potencialmente compartida que no se conoce completamente, pero de la que definitivamente se tiene conocimiento con indicios y certezas.

1. Universidad Pontificia Bolivariana. Medellín, Colombia. Correo: mateo.lopezt@upb.edu.co - https://orcid.org/0009-0000-1645-8014
2. Universidad Pontificia Bolivariana. Medellín, Colombia. Correo: valentina.deh@upb.edu.co - https://orcid.org/0009-0003-3000-546X
3. Universidad Pontificia Bolivariana. Medellín, Colombia. Correo: sofiagutierrezv@upb.edu.co - https://orcid.org/0009-0008-6392-4717
4. Universidad Pontificia Bolivariana. Medellín, Colombia. Correo: daniela.ortizp@upb.edu.co - https://orcid.org/0000-0001-6789-4561
5. Universidad Pontificia Bolivariana. Medellín, Colombia. Correo: valeria.vasqueze@upb.edu.co - https://orcid.org/0000-0001-9462-2545
6. Universidad Pontificia Bolivariana. Medellín, Colombia. Correo. paolaandrea.serna@upb.edu.co - https://orcid.org/0000-0001-8077-9461

Palabras clave: trastorno depresivo mayor; artritis reumatoide; fisiología; calidad de vida; terapéutica.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, multisystemic, inflammatory autoimmune disease. Its etiology is complex and not yet fully understood, but it involves both environmental and genetic factors. Clinically, it primarily affects synovial joints, causing inflammation, hyperplasia, diffuse pain, and cartilage and bone deformities.[1,2] It affects individuals of all ages and is associated with disability, early death, and high costs.[3] It is more prevalent in women and leads to progressive disability and susceptibility to other diseases,[4] with complications involving the lungs, kidneys, heart, eyes, and nervous system.[5]

Mood disorders such as depression and anxiety are common in patients with RA, intensifying its impact on public health and the economy.[6] Depression affects 13–20% of individuals with RA. Additionally, those with depression have a 1.70 times higher risk of developing RA, suggesting a bidirectional association.[7] The exact explanation for this relationship is still unclear, but current evidence points towards a possible shared pathophysiological basis. It appears that the proinflammatory cytokines involved in the RA disease process may affect monoaminergic neurotransmission, neurotrophic factors, and measures of synaptic plasticity,[8] potentially contributing to inflammatory consequences in the brain,[6] particularly in neuronal connectivity. The most recent studies also support the idea of a bilateral association.[6,8–10]

Given that RA and major depressive disorder (MDD) are diseases with a high impact on quality of life and functionality.6-10 This topic review summarizes the most up-to-date literature regarding their association. The aim is to raise awareness among healthcare professionals about the need to monitor the mental health of patients with RA and to conduct early detection of this rheumatologic condition in patients with MDD. As RA and MDD are linked by emerging evidence of shared mechanisms,[6-10] it is reasonable for this review also to examine the clinical approach to comorbid RA and MDD. This section is intended to complement the discussion of underlying mechanisms by summarizing studies that suggest potential common therapeutic targets and by outlining available tools for diagnosis and management of both conditions. Including this perspective aims to connect scientific understanding with practical application, highlighting pharmacological and non-pharmacological strategies that could inform integrated care.[10]

The information included in this study was obtained from PubMed. The search terms were entered directly into the search bar using the Title/Abstract field. Terms related to the diseases of interest (depression and rheumatoid arthritis) and to relevant aspects for the article (physiopathology, consequences, impact, quality of life, therapy, therapeutics, diagnosis) were combined. Articles published from January 2022 to December 2025 were selected. The search allowed discrimination by article type, and priority was given to narrative reviews, systematic reviews, meta-analyses, and clinical trials during selection. Some articles outside this search strategy that did not fall within the selected publication period were included because they were considered to make relevant contributions to the results.

Epidemiological overview of the relationship between RA and depression

RA has a high hereditary burden, and its relationship with MDD has been studied for years. In the preliminary results of a study involving 23981 parent-child pairs in which the parents had RA, and 239810 controls without RA*, Chiu et al.*[11] reported a higher risk of mental disorders in the offspring of the RA group, including MDD [Odds ratio (OR) = 1.20, 95% confidence interval (CI) 1.07 – 1.35)]. Having RA has been associated with an increased risk of developing depression by up to 66.30%.[12] The prevalence of depression in RA is two to three

times higher than in the general population, with 16.80% of patients having MDD.[13] In a review of eleven studies involving 39130 individuals with RA, 550282 with depression, and 7802230 controls, Ng *et al.*[14] reported a higher risk of depression (47%) in the first group and a higher risk of RA (34%) in the second, both compared to controls. In another study of 1004 RA patients, Englbrecht *et al.*[15] identified a prevalence of depressive symptoms in 55.40%. Although the relationship between the two conditions has been described for years, its shared impact appears to be underestimated by healthcare professionals, as the same study found that only 11.70% of individuals with depressive symptoms were receiving any form of treatment for the condition. Finally, in a study of 38487 individuals with RA and 192435 healthy controls, Jeon *et al*.[16] reported a higher risk of depression in the RA group [Adjusted hazard ratio (aHR) = 1.66, 95%CI 1.61–1.71] with no difference between seropositive RA (aHR = 1.64, 95%CI 1.58–1.69) and seronegative RA (aHR = 1.73, 95%CI 1.65–1.81).

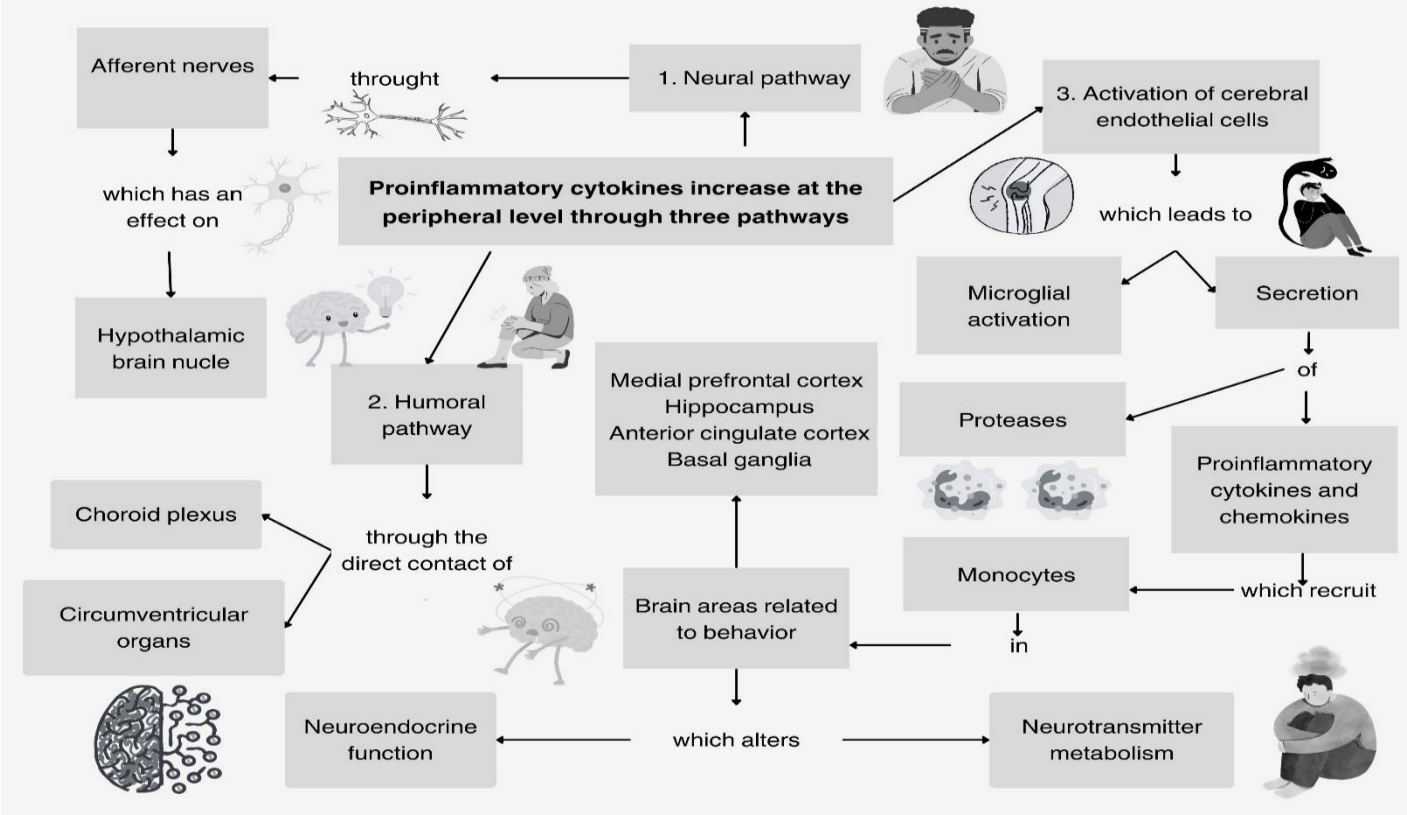

Figure 1. Pathophysiological relationship between RA and MDD based on the role of proinflammatory cytokines.

Shared pathophysiological mechanisms

The bidirectional association between the two conditions has been linked to shared pathophysiological factors, including immune dysregulation, aberrant inflammation, and involvement of serotonergic and glutamatergic pathways.[8,14,17] Similarities have been described between the neural networks involved in RA-related inflammation and those associated with depression.[13] Peripheral immune activation interacting with the central nervous system supports an immune-mediated mechanism common to both conditions,[8] potentially contributing to a vicious cycle. Elevated levels of interleukin-6 (IL-6),[18] interleukin-1 (IL-1), and tumor necrosis factor-alpha (TNF-α),[19] have been reported to be significantly higher in RA patients with

depression compared to those with RA alone. Figure 1 illustrates how proinflammatory cytokines in RA may contribute to depression.

The idea of a shared inflammatory basis is supported by a study of 4136 patients in which Shand *et al.*[20] found significantly higher rates of depression, obesity, and hypertriglyceridemia in individuals with RA ($p < 0.01$). Similarly, in a study of 120 RA patients, 36.67% of whom had comorbid MDD, Ren *et al.*[21] found elevated serum levels of indoleamine 2,3-dioxygenase, interferon-gamma (IFN-γ), and kynurenine, along with decreased tryptophan levels. In murine models of RA, they observed that depressive-like symptoms were reversed by injecting neutralizing antibodies against IFN-γ. They also identified elevated quinolinic acid levels and overactivation of N-methyl-D-aspartate (NMDA) receptors as a potential common pathophysiological pathway.

The findings remain controversial. In a Mendelian randomization study, Xiang *et al.*[22] failed to demonstrate a causal effect of proinflammatory cytokines on the presence of depression. However, most studies support the idea of a shared inflammatory pathophysiological basis. In another study of 118 RA patients and 50 healthy *controls, Smesan et al*.[23] found that 69.70% of the shared origin could be explained by immune-mediated inflammatory mechanisms such as rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA), the cluster of differentiation 17 (CD17) cell surface marker, and levels of the mu-opioid receptor.

Studies have also emphasized the search for a shared genetic basis. In a study of 45 patients with bipolar depression, 27 with unipolar depression, and 22 healthy *controls,* Dmitrzak-Węglarz *et al*.[24] investigated gene expression alterations related to RA. They found decreased expression of 35 genes, mainly the opioid receptor mu (OPRM1), and overexpression of 58 genes, primarily toll-like receptor 4 (TLR4). Specifically, in the unipolar depression group, the most overexpressed gene was tyrosine kinase with immunoglobulin-like and epidermal growth factor-like domains 2 (TEK/TIE2). In contrast, in the bipolar group, it was chemokine (C-X-C motif) ligand 8 (CXCL8). In another study, Zhou et al. identified six potential diagnostic and therapeutic markers in patients with comorbid RA and MDD: aurora kinase A (AURKA), butyrophilin subfamily three member A2 (BTN3A2), endoplasmic reticulum aminopeptidase 2 (ERAP2), phospholipase A2 group 7 (PLA2G7), c-x-c motif chemokine ligand 10 (CXCL10), and macrophage receptor with collagenous structure (MARCO), the last two being associated with immune cell diversity in RA.[7]

Attempts to elucidate this relationship have also included exploration of brain function. In a murine model of collagen antibody-induced arthritis, Wu et al. reported the emergence of behaviors resembling those seen in patients with depression, including hyperactivity, and gene expression alterations consistent with cerebrovascular disruption in the lateral habenula, an area involved in processing negative stimuli. They also found that inhibiting this area was associated with alleviation of depressive symptoms and promoted remission of arthritis, suggesting a potential therapeutic target.[25]

Impact of comorbidity on quality of life

The bidirectional relationship between the two conditions is associated with a worse natural course. Depression has been associated with poorer prognosis of RA and with higher levels of pain, fatigue, dysfunction, comorbidities, mortality, and resource expenditure.[13] In a study of 400 people with RA, Henkemans *et al.*[26] reported that 20% had scores above seven on the Hospital Anxiety and Depression Scale (HADS). Specifically, the depression component of this tool was associated with a lower likelihood of disease remission over 2 years of follow-up (OR = 0.45, 95%CI 0.25–0.80). Similarly, in a meta-analysis of 71 studies, Sweeney *et al.*[27] found that affective distress in RA patients is associated with lower remission rates, as

measured by the Disease Activity Score (DAS-28).[27] In another study of 3579 RA patients, Rojas-Gualdrón *et al*.[28] reported a loss of 8.10 months of quality-adjusted life per year lived among those with depression and severe pain.

Depression in patients with RA is further associated with lower treatment adherence, increased mortality, and higher suicide risk. Moreover, it is associated with greater healthcare utilization and costs, both direct (hospitalizations) and indirect (productivity losses). Psychiatric disorders, especially MDD, are associated with reduced life expectancy in these patients.[9,13] Emotional stress in RA has been associated with lower physical activity, reduced productivity, adverse effects on interpersonal relationships, and decreased response to immunomodulatory drugs. Depression has been linked to greater fatigue, lower treatment efficacy, and increased disability. DiRenzo *et al.*29 found that depression and anxiety scores correlated with poorer quality of life in patients with RA. Matcham *et al.,*[30] in 379 patients, demonstrated that either depression or anxiety predicted disease activity, disability, and reduced the efficacy of prednisolone over two years of follow-up. In another study of 212 RA patients, Khadour *et al.*[31] found that those with comorbid depression and/or anxiety had higher scores on the Health Assessment Questionnaire (HAQ) and the DAS-28 compared to those without mental comorbidity, which suggests that MDD may contribute to a worse disease course in patients with RA.

Pain plays a central role in the RA-MDD relationship, as patients tend to catastrophize it, which impacts their well-being and quality of life, especially due to a lack of emotional coping tools.[32] Furthermore, up to 80% of patients with RA experience sleep disorders, which are linked to worse prognosis. Chronic insomnia has been associated with increased risk of mortality, and symptoms such as intense joint pain are related to impaired sleep quality, reducing overall quality of life and daytime functioning.[33]

A clinical approach to patients with MDD and RA: coordinated treatment

The clinical management of patients with RA and depression is challenging, as mental illness is associated with reduced effectiveness of autoimmune disease treatment. In a study of 5502 RA patients, including 511 with comorbid depression, Manning-Bennett *et al*.[34] reported that mental illness was associated with lower remission rates according to two RA activity scores: the Clinical Disease Activity Index (CDAI) [Hazard ratio (HR) = 0.62, 95%CI 0.48–0.80] and the Simplified Disease Activity Index (SDAI) (HR = 0.59, 95%CI 0.44–0.79). For this reason, RA patients require additional care, and it is crucial to address their mental health. Several psychological interventions are associated with reductions in pain and improvements in emotional well-being, including cognitive-behavioral therapy (CBT), acceptance and commitment therapy, and practices such as meditation, yoga, and tai chi.[35]

In 2022, the American College of Rheumatology included, in its 28 recommendations, the use of cognitive-behavioral psychotherapy (supported by low-quality evidence) to improve pain and physical function, and, by low to moderate-quality evidence, to improve depression, anxiety, fatigue, and sleep disorders.[36] The need to strengthen this evidence has driven studies to focus on how psychiatric interventions may influence the course of RA. Almodóvar *et al*.[37] emphasized the importance of clinical trials on duloxetine and milnacipran in patients with residual pain and RA in remission. Menzies *et al.*[38] proposed a trial with 300 patients to compare CBT and mindfulness-based stress reduction (MBSR). Previous studies suggest that the first has been associated with greater impact on RA-related pain and inflammation, while the latter appears to improve psychological functioning in recurrent depression.[38]

RA has also been associated with challenges in depression treatment. In a Mendelian randomization study, Wan *et al.* [39] found that genetic liability for RA was associated with increased antidepressant requirements

(Beta = 0.03, p = 0.01), reinforcing the notion that both diseases may amplify each other. Due to their bidirectional relationship, it is essential to explore a shared biological component. In 2024, Fu *et al.*[18] compared immunological markers in 46 patients with RA and depression and 53 with RA alone and found higher levels of interleukin-16 (IL-16) and T helper 17 (Th17) lymphocytes, and lower levels of regulatory T cells, in the first group. This finding highlights the need to consider joint therapeutic approaches. In a clinical trial involving 213 RA patients, Baghdadi *et al.*[40] found that leflunomide (p<0.01) and tocilizumab (p<0.01) were associated with reduced depression and anxiety. Etanercept was also linked to reduced depressive symptoms after adjusting for confounding factors (p=0.04).

These findings have been controversial. Improvement in depressive symptoms with biologic DMARDs has been reported, as well as their association with higher rates of depression, anxiety, and suicide compared to methotrexate, leflunomide, and hydroxychloroquine. Infliximab has shown variability, ranging from improvement to no effect, and even increased suicidal tendencies. IL-6 inhibitors such as tocilizumab have demonstrated a positive impact on depressive symptoms; others like siltuximab and sirukumab, although associated with more adverse events, may benefit patients with refractory RA.[41] In a post hoc analysis of two trials including 4404 patients, *Citera et al.*[42] reported depression or anxiety in 44.50%, 39.80%, 45.40%, and 39.10% of those receiving five mg of tofacitinib every 12 h, ten mg of tofacitinib every 12 h, adalimumab, and placebo, respectively. Improvement in depression and anxiety symptoms was observed with tofacitinib compared to adalimumab and placebo, suggesting its potential for joint treatment.

Future directions for research

The lack of consensus presents an opportunity for future studies to establish standardized recommendations for immunomodulators in patients with RA and depression.[8] There is a need not only to improve pharmacological treatment with therapeutic evidence but also to adapt care programs. In a study of 224 patients with active seropositive RA, Hoepner *et al.*[43] assessed the impact of visits by rheumatology assistants trained in mental illness. Although no differences were found in depression scales (p=0.86), patient satisfaction was significantly higher at six (p=0.01) and 12 months (p<0.01) in the intervention group. Perez-Sousa *et al.*[44] evaluated a 12-week aquatic exercise program in 21 RA patients versus 23 controls. Greater effects were observed in pain control and moderate effects in depressive symptoms, suggesting that pain management may be associated with improvements in affective symptoms. This observation underscores the need to strengthen multidisciplinary programs and assess psychological and integrative interventions to determine their cost-effective impact on the disease.

Future research should also clarify whether specific immunomodulators differ in their neuropsychiatric effects,[40-42] explore biomarkers that predict treatment response in comorbid depression,[18] and determine how early interventions targeting fatigue, sleep, or pain perception influence long-term mental health outcomes. Likewise, randomized controlled trials with adequate power and longer follow-up are necessary to establish whether non-pharmacological interventions translate into sustained reductions in depressive symptoms and disability.[35-38]

A clinical approach to patients with MDD and RA: Coordinated diagnosis

Regarding the diagnosis of both diseases, it is essential to emphasize that depression screening in RA patients should combine clinical judgment with standardized self-report tools such as the Patient Health Questionnaire-9 (PHQ-9)[45] and Beck Depression Inventory-II (BDI-II).46 While the Hamilton Rating Scale for Depression-17 (HAMD-17) remains a research standard.[45] The PHQ-9 shows high agreement with HAMD-17,

making it practical for routine clinical use.[45] The BDI-II is useful to grade baseline severity and track changes over time in observational or treatment studies.[46] In contrast, the Multidimensional Health Assessment Questionnaire (MDHAQ) is not a diagnostic tool for depression. Still, its mood-related items help explain elevated patient global assessment scores that are unrelated to inflammatory activity.[47] After a positive screening result in these patients, DSM-5 criteria for major depressive disorder should be applied. Theses indicate that MDD is diagnosed when five or more symptoms are present during the same two-week period, representing a change from previous functioning, and at least one is depressed mood or loss of interest/pleasure: depressed mood; diminished interest; significant weight/appetite change; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue; feelings of worthlessness or guilt; concentration difficulties; or suicidal ideation. Symptoms must cause significant distress or impairment and cannot be explained by substances, medical conditions, or other psychiatric disorders. A detailed review of therapeutic strategies for a depressive episode is beyond the scope of this manuscript.[48]

RA diagnosis in patients with MDD is made in the same way as in any other patient. The initial workup includes C-reactive protein (CRP), RF, ACPA[49], complete blood count (CBC), and erythrocyte sedimentation rate (ESR) to document systemic inflammation and autoimmunity. If results suggest active inflammations, additional tests are performed to assess potential organ involvement and future treatment safety, such as liver transaminases, serum creatinine, and urinalysis. Finally, the diagnosis is determined by applying the 2010 Classification Criteria of the American College of Rheumatology and the European League Against Rheumatism (ACR–EULAR 2010). These require the presence of clinical synovitis in at least one joint, not better explained by another disease, and use a scoring system in four domains. Joint involvement accounts for up to five points, with higher scores assigned when multiple small joints are affected. Serology (RF and ACAP) contributes zero to three points depending on whether tests are negative, less than three times above the upper limit of normal, or more than three times above the upper limit of normal. Acute-phase reactants (elevated ESR or CRP) add 1 point, and symptom duration of 6 weeks or more adds another point. A total score of six or more out of ten classifies a patient as having RA.[50,51] On the other hand, the Leiden prediction rule estimates the likelihood that early undifferentiated arthritis will progress to rheumatoid arthritis. Using clinical, serological, and inflammatory variables to generate a risk score helps identify patients who may benefit from earlier treatment to prevent joint damage.[52]

Points of controversy

A valid point of controversy arising from the proposed information is why some TNF inhibitors improve depressive symptoms while others appear to worsen them. Improvement in depressive symptoms with specific TNF inhibitors has been attributed to modulation of amygdala reactivity and normalization of serotonergic homeostasis in the brain, resulting in reduced depressive symptomatology in some patients.[53-55] However, not all TNF inhibitors can cross the blood brain barrier or modulate the neuroimmune pathways implicated in depression, and RA related depression is not exclusively driven by systemic inflammation; chronic pain, functional disability, psychosocial stress, and genetic vulnerability also play relevant roles.[54,56,57] Taken together, these factors suggest that the antidepressant effect of TNF inhibitors depends on their specific neuroimmune actions and their ability to influence central inflammatory pathways, meaning that treatments that act mainly on peripheral inflammation may not provide the same neuropsychiatric benefit and may even aggravate symptoms in certain patients.[58,59]

Another point of controversy arises from the observation that, despite a proposed shared pathophysiological basis, only 13–20% of patients with RA develop depression. This point suggests that the relationship reflects

correlation rather than a defined causal link, and additional factors are required for one condition to lead to the other. Depression emerges from the convergence of multiple risk factors, not inflammation alone. Individual variability in genetic susceptibility, psychosocial environment, pain control, and treatment response further modulates the risk of developing depression. [54,56,57] In this context, RA can be considered a biological stressor that contributes to a vulnerable neuroimmune background, but depression only manifests when predisposing and precipitating factors align. Clinically, this highlights the importance of comprehensive screening for psychological symptoms in RA, as effective management requires addressing not only inflammation, but also pain, function, and psychosocial burden. [60-62]

CONCLUSIONS

MDD and RA are associated. Recent evidence points to a shared pathophysiological basis, involving proinflammatory cytokines, common genes, and dysfunction in brain regions that process emotions. When combined, the two diseases have a far greater impact on patients' lives than either would have alone. Depression is associated with pain catastrophizing in RA, worsens the disease course, interferes with treatment response, and affects sleep. The significant relationship between the two conditions makes pursuing common therapeutic targets the most reasonable direction for future research. Ideally, all rheumatology departments should have physicians trained in the management of mental illness to provide comprehensive care. Psychotherapy is beneficial for patients with both RA and MDD. In the future, psychiatric medications may have evidence supporting their use for clinical manifestations of RA, while antirheumatic drugs could potentially demonstrate benefits in managing depressive symptoms in RA patients. Therefore, physicians should actively screen for depressive symptoms in all RA patients and consider RA as a potential diagnosis in MDD patients presenting with suggestive signs and symptoms.

DECLARATION OF CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

FUNDING STATEMENT

The authors declare that they received no funding for this work.

AUTHOR CONTRIBUTIONS

MLT participated in conceptualization, literature review, study design proposal, drafting, and final approval of the manuscript.
VDAH participated in conceptualization, literature review, study design proposal, drafting, and final approval of the manuscript.
SGV participated in conceptualization, literature review, study design proposal, drafting, and final approval of the manuscript.
DOP participated in conceptualization, literature review, study design proposal, drafting, and final approval of the manuscript.
VVE participated in conceptualization, literature review, study design proposal, drafting, and final approval of the manuscript.
PASJ participated in drafting and final approval of the manuscript.

REFERENCES

1. Díaz F, Hernández MV. Artritis reumatoide [Rheumatoid arthritis]. Med Clin (Barc). 2023;161:533–42. https://doi.org/10.1016/j.medcli.2023.07.014

2. Jang S, Kwon EJ, Lee JJ. Rheumatoid arthritis: Pathogenic roles of diverse immune cells. Int J Mol Sci. 2022;23:905. https://doi.org/10.3390/ijms23020905

3. Di Matteo A, Bathon JM, Emery P. Rheumatoid arthritis. Lancet. 2023;402:2019–33. https://doi.org/10.1016/S0140-6736(23)01525-8

4. Miguel D, Elizararrás J, Villarreal E, Baltiérrez R, Velasco U, Vargas ER, et al. Perfil epidemiológico de la artritis reumatoide [Epidemiological profile of rheumatoid arthritis]. Rev Med Inst Mex Seguro Soc. 2023;61:574–82. https://doi.org/10.5281/zenodo.8316427

5. Wu D, Luo Y, Li T, Zhao X, Lv T, Fang G, et al. Systemic complications of rheumatoid arthritis: Focus on pathogenesis and treatment. Front Immunol. 2022;13:1051082. https://doi.org/10.3389/fimmu.2022.1051082

6. Geng Y, Gao T, Zhang X, Wang Y, Zhang Z. The association between disease duration and mood disorders in rheumatoid arthritis patients. Clin Rheumatol. 2022;41:661–8. https://doi.org/10.1007/s10067-021-05967-2

7. Zhou TT, Sun JJ, Tang LD, Yuan Y, Wang JY, Zhang L. Potential diagnostic markers and therapeutic targets for rheumatoid arthritis with comorbid depression based on bioinformatics analysis. Front Immunol. 2023;14:1007624. https://doi.org/10.3389/fimmu.2023.1007624

8. Brock J, Basu N, Schlachetzki JCM, Schett G, McInnes IB, Cavanagh J. Immune mechanisms of depression in rheumatoid arthritis. Nat Rev Rheumatol. 2023;19:790–804. https://doi.org/10.1038/s41584-023-01037-w

9. Lwin MN, Serhal L, Holroyd C, Edwards CJ. Rheumatoid Arthritis: The Impact of Mental Health on Disease: A Narrative Review. Rheumatol Ther. 2020;7:457–71. https://doi.org/10.1007/s40744-020-00217-4

10. Pham HT, Vu-Thi H, Le CT, Dau QL, Nguyen MD, Nguyen-Van H. Characteristics of depressive disorders in patients with rheumatoid arthritis and some related factors. Eur Rev Med Pharmacol Sci. 2024;28:255–62. https://doi.org/10.26355/eurrev_202401_34911

11. Chiu HJ, Sun CK, Tsai SJ, Bai YM, Hung KC, Hsu JW, et al. A nationwide study of the risks of major mental disorders among the offspring of parents with rheumatoid arthritis. Sci Rep. 2022;12:4962. https://doi.org/10.1038/s41598-022-08834-5

12. Stanciu I, Anderson J, Siebert S, Mackay D, Lyall DM. Associations of rheumatoid arthritis and rheumatoid factor with mental health, sleep and cognition characteristics in the UK Biobank. Sci Rep. 2022;12:19844. https://doi.org/10.1038/s41598-022-22021-6

13. Ionescu CE, Popescu CC, Agache M, Dinache G, Codreanu C. Depression in rheumatoid arthritis: Prevalence and effects on disease activity. J Clin Med. 2024;13:2058. https://doi.org/10.3390/jcm13072058

14. Ng CYH, Tay SH, McIntyre RS, Ho R, Tam WWS, Ho CSH. Elucidating a bidirectional association between rheumatoid arthritis and depression: A systematic review and meta-analysis. J Affect Disord. 2022;311:407–15. https://doi.org/10.1016/j.jad.2022.05.108

15. Englbrecht M, Alten R, Aringer M, Baerwald CG, Burkhardt H, Eby N, et al. New insights into the prevalence of depressive symptoms and depression in rheumatoid arthritis - Implications from the prospective multicenter VADERA II study. PLoS One. 2019;14:e0217412. https://doi.org/10.1371/journal.pone.0217412

16. Jeon KH, Han K, Jung J, Park CI, Eun Y, Shin DW, et al. Rheumatoid arthritis and risk of depression in South Korea. JAMA Netw Open. 2024;7:e241139. https://doi.org/10.1001/jamanetworkopen.2024.1139

17. Gao D, Gao X, Yang F, Wang Q. Neuroimmune crosstalk in rheumatoid arthritis. Int J Mol Sci. 2022;23:8158. https://doi.org/10.3390/ijms23158158

18. Fu T, Liu Y, Jia H, Yao L, Zhang S, Tian F. Analysis of potential diagnostic markers and therapeutic targets for rheumatoid arthritis with comorbid depression immunologic indicators. Behav Brain Res. 2024;471:115098. https://doi.org/10.1016/j.bbr.2024.115098

19. Sharma A, Goel A. Inflammatory cytokines in rheumatoid arthritis: Diagnostic challenges, pathogenic mechanisms and their role in depression and management. Curr Top Med Chem. 2023;23:2535-51. https://doi.org/10.2174/1568026623666230915095151

20. Shand G, Fuller DT, Lufkin L, Lovelett C, Pal N, Mondal S, et al. A stronger association of depression with rheumatoid arthritis in presence of obesity and hypertriglyceridemia. Front Epidemiol. 2023;3:1216497. https://doi.org/10.3389/fepid.2023.1216497

21. Ren H, Lin F, Wu L, Tan L, Lu L, Xie X, et al. The prevalence and the effect of interferon-γ in the comorbidity of rheumatoid arthritis and depression. Behav Brain Res. 2023;439:114237. https://doi.org/10.1016/j.bbr.2022.114237

22. Xiang S, Xu D, Jin Y, Wang R, Wen C, Ding X. The role of inflammatory biomarkers in the association between rheumatoid arthritis and depression: A Mendelian randomization study. Inflammopharmacology. 2023;31:1839-48. https://doi.org/10.1007/s10787-023-01241-w

23. Smesam HN, Qazmooz HA, Khayoon SQ, Almulla AF, Al-Hakeim HK, Maes M. Pathway phenotypes underpinning depression, anxiety, and chronic fatigue symptoms due to acute rheumatoid arthritis: A precision nomothetic psychiatry analysis. J Pers Med. 2022;12:476. https://doi.org/10.3390/jpm12030476

24. Dmitrzak-Węglarz M, Rybakowski J, Szczepankiewicz A, Kapelski P, Lesicka M, Jabłońska E, et al. Identification of shared disease marker genes and underlying mechanisms between major depression and rheumatoid arthritis. J Psychiatr Res. 2023;168:22–9. https://doi.org/10.1016/j.jpsychires.2023.10.036

25. Wu P, Li W, Lv R, Cheng X, Lian F, Cai W, et al. Hyperactive lateral habenula mediates the comorbidity between rheumatoid arthritis and depression-like behaviors. Brain Behav Immun. 2024;117:412–27. https://doi.org/10.1016/j.bbi.2024.02.006

26. Snoeck Henkemans SVJ, Vis M, Koc GH, Luime JJ, Kok MR, Tchetverikov I, et al. Association between depression and anxiety and inability to achieve remission in rheumatoid arthritis and psoriatic arthritis. Rheumatology. 2024:keae621. https://doi.org/10.1093/rheumatology/keae621

27. Sweeney M, Adas MA, Cope A, Norton S. Longitudinal effects of affective distress on disease outcomes in rheumatoid arthritis: A meta-analysis and systematic review. Rheumatol Int. 2024;44:1421–33. https://doi.org/10.1007/0296-024-05574-9

28. Rojas-Gualdrón DF, Franco-Salazar C, Gómez-Henck CÁ, Manrique-Castrillón MC, Hoyos-Méndez YC, Vélez-Romero S, et al. Health-related quality of life (HRQoL) loss associated with self-perceived anxiety/depression in seropositive rheumatoid arthritis. Clin Rheumatol. 2024;43:3647–55. https://doi.org/10.1007/s10067-024-07186-x

29. DiRenzo DD, Craig ET, Bingham III CO, Bartlett SJ. Anxiety impacts rheumatoid arthritis symptoms and health-related quality of life even at low levels. Clin Exp Rheumatol. 2020;38:1176–81.

30. Matcham F, Norton S, Scott DL, Steer S, Hotopf M. Symptoms of depression and anxiety predict treatment response and long-term physical health outcomes in rheumatoid arthritis: secondary analysis of a randomized controlled trial. Rheumatology (Oxford). 2016;55:268-78. https://doi.org/10.1093/rheumatology/kev306.

31. Khadour FA, Khadour YA, Ebrahem BM. A qualitative survey on factors affecting depression and anxiety in patients with rheumatoid arthritis: A cross-sectional study in Syria. Sci Rep. 2024;14:11513. https://doi.org/10.1038/s41598-024-61523-3

32. Wilk M, Zimba O, Haugeberg G, Korkosz M. Pain catastrophizing in rheumatic diseases: Prevalence, origin, and implications. Rheumatol Int. 2024;44:985–1002. https://doi.org/10.1007/s00296-024-05583-8

33. Tański W, Świątoniowska-Lonc N, Tomasiewicz A, Dudek K, Jankowska-Polańska B. The impact of sleep disorders on the daily activity and quality of life in rheumatoid arthritis patients - a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci. 2022;26:3212–29. https://doi.org/10.26355/eurrev_202205_28740

34. Manning-Bennett AT, Hopkins AM, Sorich MJ, Proudman SM, Foster DJR, Abuhelwa AY, et al. The association of depression and anxiety with treatment outcomes in patients with rheumatoid arthritis - A pooled analysis of five randomised controlled trials. Ther Adv Musculoskelet Dis. 2022;14:1759720X221111613. https://doi.org/10.1177/1759720X221111613

35. Bekarissova S, Bekarisov O, Bekaryssova D. An integrated approach to the treatment of rheumatic diseases: The role of psychological interventions. Rheumatol Int. 2024;44:2727–35. https://doi.org/10.1007/s00296-024-05728-9

36. England BR, Smith BJ, Baker NA, Barton JL, Oatis CA, Guyatt G, et al. 2022 American College of Rheumatology guideline for exercise, rehabilitation, diet, and additional integrative interventions for rheumatoid arthritis. Arthritis Rheumatol. 2023;75:1299–311. https://doi.org/10.1002/art.42507

37. Silva Almodóvar A, Nguyen D, Nahata MC. Evidence Needed for efficacy of antidepressant medications among patients with rheumatoid arthritis. Ann Pharmacother. 2022;56:1065–75. https://doi.org/10.1177/10600280211062271

38. Menzies RE, Sharpe L, Richmond B, Dudeney J, Todd J, Szabo M, et al. Randomised controlled trial of cognitive behaviour therapy versus mindfulness for people with rheumatoid arthritis with and without a history of recurrent depression: Study protocol and design. BMJ Open. 2022;12:e056504. https://doi.org/10.1136/bmjopen-2021-056504

39. Wan X, Xie J, Yang M, Yu H, Hou W, Xu K, et al. Does having rheumatoid arthritis increase the dose of depression medications? A Mendelian randomization study. J Clin Med. 2023;12:1405. https://doi.org/10.3390/jcm12041405

40. Baghdadi LR, Alhassan MK, Alotaibi FH, Alsuwaida AA, Shehadah AE, Alzahrani MT. Effect of type of disease-modifying antirheumatic drugs on depression and anxiety of patients with rheumatoid arthritis in Saudi Arabia: A cross-sectional study. Front Psychiatry. 2023;14:1184720. https://doi.org/10.3389/fpsyt.2023.1184720

41. Liu N, Yan W, Su R, Zhang L, Wang X, Li Z, et al. Research progress on rheumatoid arthritis-associated depression. Front Behav Neurosci. 2023;16:992223. https://doi.org/10.3389/fnbeh.2022.992223

42. Citera G, Jain R, Irazoque F, Madariaga H, Gruben D, Wang L, et al. Tofacitinib efficacy in patients with rheumatoid arthritis and probable depression/anxiety: Post hoc analysis of phase 3 and 3b/4 randomized controlled trials. Rheumatol Ther. 2024;11:35–50. https://doi.org/10.1007/s40744-023-00612-7

43. Hoeper JR, Schuch F, Steffens-Korbanka P, Gauler G, Welcker M, Wendler J, et al. Delegation of medical duties to qualified rheumatology assistants: Effect on depression and anxiety in patients with rheumatoid arthritis. Z Rheumatol. 2024;83:407–15. https://doi.org/10.1007/s00393-023-01403-9

44. Perez-Sousa MA, Pedro J, Carrasco-Zahinos R, Raimundo A, Parraca JA, Tomas-Carus P. Effects of aquatic exercises for women with rheumatoid arthritis: A 12-week intervention in a quasi-experimental study with pain as a mediator of depression. Int J Environ Res Public Health. 2023;20:5872. https://doi.org/10.3390/ijerph20105872

45. Li F, Ai W, Ye J, Wang C, Yuan S, Xie Y, et al. Inflammatory markers and risk factors of RA patients with depression and application of different scales in judging depression. Clin Rheumatol. 2022;41:2309–17. https://doi.org/10.1007/s10067-022-06174-3

46. Behrens F, Burmester GR, Feuchtenberger M, Kellner H, Kuehne C, Liebhaber A, et al. Characterisation of depressive symptoms in rheumatoid arthritis patients treated with tocilizumab during routine daily care. Clin Exp Rheumatol. 2022;40:551–9. https://doi.org/10.55563/clinexprheumatol/yu55rd

47. Schmukler J, Li T, Gibson KA, Morla RM, Luta G, Pincus T. Patient global assessment is elevated by up to 5 of 10 units in patients with inflammatory arthritis who screen positive for fibromyalgia (by FAST4) and/or depression (by MDS2) on a single MDHAQ. Semin Arthritis Rheum. 2023;58:152151. https://doi.org/10.1016/j.semarthrit.2022.152151

48. Lundin A, Möller J, Forsell Y. The Major Depression Inventory for diagnosing according to DSM-5 and ICD-11: Psychometric properties and validity in a Swedish general population. Int J Methods Psychiatr Res. 2023;32:e1966. https://doi.org/10.1002/mpr.1966

49. Peterson E, Gallagher MK, Wilbur J. Rheumatoid arthritis: Diagnosis and management for the family physician. Am Fam Physician. 2024;110:515–26.

50. Fautrel B, Kedra J, Rempenault C, Juge PA, Drouet J, Avouac J, et al. 2024 update of the recommendations of the French Society of Rheumatology for the diagnosis and management of patients with rheumatoid arthritis. Joint Bone Spine. 2024;91:105790. https://doi.org/10.1016/j.jbspin.2024.105790

51. Sahin D, Di Matteo A, Emery P. Biomarkers in the diagnosis, prognosis and management of rheumatoid arthritis: A comprehensive review. Ann Clin Biochem. 2024:45632241285843. https://doi.org/10.1177/00045632241285843

52. Boeters DM, Gaujoux-Viala C, Constantin A, van der Helm-van Mil AHM. The 2010 ACR/EULAR criteria are not sufficiently accurate in the early identification of autoantibody-negative rheumatoid arthritis: Results from the Leiden-EAC and ESPOIR cohorts. Semin Arthritis Rheum. 2017;47:170-4. https://doi.org/10.1016/j.semarthrit.2017.04.009

53. Davies KA, Cooper E, Voon V, Tibble J, Cercignani M, Harrison NA. Interferon and anti-TNF therapies differentially modulate amygdala reactivity which predicts associated bidirectional changes in depressive symptoms. Mol Psychiatry. 2021;26:5150-60. https://doi.org/10.1038/s41380-020-0790-9

54. McInnes IB, Schett G. Pathogenetic insights from the treatment of rheumatoid arthritis. Lancet. 2017;389:2328-2337. https://doi.org/10.1016/S0140-6736(17)31472-1

55. Krishnadas R, Nicol A, Sassarini J, Puri N, Burden AD, Leman J, et al. Circulating tumour necrosis factor is highly correlated with brainstem serotonin transporter availability in humans. Brain Behav Immun. 2016;51:29-38. https://doi.org/10.1016/j.bbi.2015.08.005

56. Siuchnińska H, Minarowska A, Wasilewska E. Beyond Joints: Neuropsychiatric Benefits of TNF-α and IL-6 Inhibitors in Rheumatoid Arthritis-Narrative Review. Int J Mol Sci. 2025;26:8361. https://doi.org/10.3390/ijms26178361

57. Lopes F, Vicentini FA, Cluny NL, Mathews AJ, Lee BH, Almishri WA, et al. Brain TNF drives post-inflammation depression-like behavior and persistent pain in experimental arthritis. Brain Behav Immun. 2020;89:224-32. https://doi.org/10.1016/j.bbi.2020.06.023

58. Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: The role of baseline inflammatory biomarkers. JAMA Psychiatry. 2013;70:31-41. https://doi.org/10.1001/2013.jamapsychiatry.4

59. Lee Y, Mansur RB, Brietzke E, Kapogiannis D, Delgado-Peraza F, Boutilier JJ, et al. Peripheral inflammatory biomarkers define biotypes of bipolar depression. Mol Psychiatry. 2021;26:3395-406. https://doi.org/10.1038/s41380-021-01051-y

60. Husakova M, Balajkova V, Pavelka K, Senolt L, Kuchaříková K, Mohr P, et al. Mental health in patients with rheumatoid arthritis and axial spondyloarthritis: a cross-sectional, case-control tertiary centre study from Czechia. BMJ Open. 2025;15:e103686. https://doi.org/10.1136/bmjopen-2025-103686

61. Vergne-Salle P, Pouplin S, Trouvin AP, Bera-Louville A, Soubrier M, Richez C, et al. The burden of pain in rheumatoid arthritis: Impact of disease activity and psychological factors. Eur J Pain. 2020;24:1979-89. https://doi.org/10.1002/ejp.1651

62. Zartaloudi A, Alexos E, Mastrogiannis D, Marinaki D, Athanasiadou E, Kalogianni A. Depression in Patients with Rheumatoid Arthritis: Unmasking the Hidden Burden. Adv Exp Med Biol. 2026;1487:63-70. https://doi.org/10.1007/978-3-032-03398-7_8