Ciências Biológicas

***Scientia Amazonia*, v. 12, n.2, B18-B25, 2023**
Revista on-line http://www.scientia-amazonia.org
https://doi.org/10.5281/zenodo.8317183 -ISSN:2238.1910

Depression and anxiety are triggers for Rheumatoid Arthritis?A Systematic Review Protocol

Nathalie Marte Ureña[1], Márcia de Lorena Serra Maia[2], Maria Cristina dos Santos[3], Antônio Luiz Ribeiro Boechat[4], Silvania da Conceição Furtado[5]

Abstract

Background: Rheumatoid Arthritis is a systemic autoimmune disease that affects 1% of the world population. These patients have a higher prevalence of mental disorders. The bidirectional association between mental disorders and autoimmunity may be explained by the interaction of proinflammatory cytokines with specific areas of the brain. But to this date, no systematic review associates depression and anxiety as risk factors for Rheumatoid Arthritis. The aim of this systematic review is to analyze the current evidence on this issue. Methods: This protocol follows the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The search will be carried out in the following databases: Medline/PubMed, Embase, Scopus, Web of Science, LILACS, Cochrane Library, PsycInfo and ProQuest. We will include cohort and case-control studies of the adult population that make an association between depression, anxiety and Rheumatoid Arthritis. The extraction of the data will be performed after the full reading of the articles and inclusion based on the eligibility criteria. To assess the risk of bias the Newcastle-Ottawa Scale will be used. Discussion: The results of this systematic review seek to fill in the knowledge gaps in this area of psychoneuroimmunology and bring information to help specialists and researchers. Ethics and dissemination: Does not require ethics committee approval as the work involves searching data already published in existing databases. The electronic publication of this Systematic Review will be in a peer-reviewed journal. Systematic review record in PROSPERO: CRD42023404169.

Keywords: psychoneuroimmunology, rheumatoid arthritis, depression, anxiety, systematic review

Depressão e ansiedade são gatilhos para a Artrite Reumatoide? Protocolo de uma Revisão Sistemática. Introdução: A Artrite Reumatoide é uma doença autoimune sistêmica que afeta 1% da população mundial. Esta população tem maior prevalência de transtornos mentais. A associação bidirecional entre transtornos mentais e autoimunidade pode ser

[1] PhD student at the Postgraduate Program of Basic and Applied Immunology (PPGIBA) at the Federal University of the Amazon (UFAM). nathaliemarte.u@gmail.com
[2] Master in Immunology by the Program of Basic and Applied Immunology (PPGIBA) of the Federal University of the Amazon (UFAM). marciadelorenasmaia@gmail.com
[3] Professor at the Postgraduate Program of Basic and Applied Immunology (PPGIBA) at the Federal University of the Amazon (UFAM). mcsantos@ufam.edu.br
[4] Professor at the Postgraduate Program of Basic and Applied Immunology (PPGIBA) at the Federal University of the Amazon (UFAM). alboechat@ufam.edu.br
[5] Professor at the Postgraduate Program of Basic and Applied Immunology (PPGIBA) at the Federal University of the Amazon (UFAM). silvaniafurtado@ufam.edu.br

Scientia Amazonia, v. 12, n.2, B18-B25, 2023
Revista on-line http://www.scientia-amazonia.org
https://doi.org/10.5281/zenodo.8317183 -ISSN:2238.1910
Ciências Biológicas

explicada pela interação de citocinas pró-inflamatórias com áreas específicas do cérebro. Mas, até o momento, nenhuma revisão sistemática associa depressão e ansiedade como fatores de risco para Artrite Reumatoide. O objetivo desta revisão sistemática é analisar as evidências atuais sobre esse assunto. Métodos: Este protocolo segue as diretrizes dos "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA). A busca será realizada nas seguintes bases de dados: Medline/PubMed, Embase, Scopus, Web of Science, LILACS, Cochrane Library, PsycInfo e ProQuest. Incluiremos estudos de coorte e caso-controle em população adulta que fazem associação entre depressão, ansiedade e Artrite Reumatoide. A extração dos dados será realizada após a leitura na íntegra dos artigos e inclusão com base nos critérios de elegibilidade. Para avaliar o risco de viés será utilizada a Escala de Newcastle-Ottawa. Discussão: Os resultados desta revisão sistemática buscam preencher as lacunas de conhecimento nesta área da psiconeuroimunologia e trazer informações para auxiliar especialistas e pesquisadores. Ética e divulgação: Não requer aprovação do comitê de ética, pois o trabalho envolve a busca de dados já publicados em bases de dados existentes. A publicação eletrônica desta Revisão Sistemática será em um periódico revisado por pares. Registro de revisão sistemática no PROSPERO: CRD42023404169.

Palavras-Chave: psiconeuroimunologia, artrite reumatoide, depressão, ansiedade, revisão sistemática

1. Introduction

Rheumatoid Arthritis (RA) is a systemic multifactorial autoimmune disease that primarily affects the joints. Approximately 1% of the world population suffers from this disease. Two countries have the higher prevalence, Japan (1.7%) and Argentina (1.97%) (Radu et al., 2021). Research shows that patients with rheumatic diseases have higher prevalence of mental disorders like depression and anxiety (Geenen et al., 2012). These patients have higher prevalence for depression (14-48%), this being the most frequent comorbidity for RA (Fakra et al., 2021). Of all mental disorders, depression has been more associated with Rheumatoid Arthritis. Literature shows that this association may come from common immune alteration in both diseases, like elevated levels of IL-1$\boldsymbol{\beta}$, TNF-$\boldsymbol{\alpha}$, IL-6 and CRP (Nerurkar et al., 2019). These cytokines can reach the brain and modulate the functions of the prefrontal cortex, hippocampus, anterior cingulate cortex and the basal ganglia; and theses areas are associated with the pathophysiology of depression (Vallerand et al., 2019).

There are three mechanisms from which the inflammatory markers of RA can reach the Central Nervous System (CNS) 1) Markers can activated the endothelium of the blood-brain barrier, 2) TNF can be actively transported to the CNS, through the blood-brain barrier and 3) inflammatory markers can reach the CNS through circumventricular organs (Pan, 2011; Schiltz, 2002). On the other side, stress disorders are associated with autoimmune diseases through the imbalance of the Hypothalamus-Pituitary-Adrenal axis (HPA) and the Autonomic Nervous System (ANS), thus being able to modulate the immune function and predisposing the individual to diseases (Song et al., 2018).

Research shows that the level of disease activity in RA is associated with the presence of mental disorders. Skinner-Taylor et al. observed higher rates of anxiety (20.8%, 12.5%) and depression (12.5%, 10.4%) in women with RA; and a furthermore significant statistical association between RA disease activity and different stages of anxiety (p=0.01) (Skinner-Taylor et al., 2020).

In another study, Lu et al. 2016, the team observed that the patients with RA had higher incidence of depression when compared with healthy controls (15.69 vs. 8.95 per 1,000 person-years [PYs]; HR 1.69). The authors also observed that patients with depression had higher risks for developing RA when compared with healthy controls (2.07 vs. 1.21 per 1,000 PYs; HR 1.65) (Lu et al., 2016). Sparks et al. 2021, observed that women with depression had higher risk of developing seronegative RA (HR 1.63, 95% CI) than seropositive RA (HR 1.12, 95% CI) (Sparks et al., 2021).

Vallerand et al. 2018, research evaluated the risk of major depression disorder (MDD) patients of developing RA. The authors observed that MDD patients had higher risk of RA (HR= 1.31, 95% CI 1.25 to 1.36, p<0.0001) (Vallerand et al., 2018). Studying stress as a trigger for RA Germain et al. 2021, observed that 54.8% patients with RA attributed the beginning of the disease to an anterior stressful event, when compared with controls. Their results shows that RA patients had higher levels of perception of stress (167.0) when compared with controls (83.3) (Germain et al., 2021).

Marrie et al. 2019 research investigated the incidence of psychiatric disorders before the diagnosis of Immune Mediated Inflammatory Diseases (IMID) like Irritable Bowel Disease (IBD), Multiple Sclerosis (MS) and Rheumatoid Arthritis (RA). The authors observed that 5 years before the diagnosis of IMID, the risk of depression (IRR 1.54; 95% CI) and anxiety (IRR 1.30; 95% CI) where higher than the healthy population. RA patients presented incidence risk of depression of IRR 2.25; 95% CI, and IRR 1.42; 95% CI for anxiety (Marrie et al., 2019).

Literature shows the bidirectional relationship between mental disorders and Rheumatoid Arthritis. It is still necessary to elucidate the pathophysiological mechanisms by which psychological disorders modulate immune function, and to deepen the potential risk that these disorders may have in the development of immune diseases.

2. Methodology

2.1 Protocol Register

The protocol was registered in the International Prospective Registry of Systematic Reviews (PROSPERO) with the number CRD42023404169.

2.2 Eligibility Criteria

Based on our question: Can psychological disorders of depression and anxiety be considered risk factors for Rheumatoid Arthritis?

We will include cohort and case-control studies that make some kind of association between depression and/or anxiety and RA.

- Studies carried out with participants over 18 years of age.
- Studies that assess the presence of depression and/or anxiety with any of the following inventories validated by the Psychological Test Assessment System (SATEPSI) and American Psychological Association (APA): Beck Depression Inventory II (BDI-II), Montgomery-Asberg Depression Scale (MSDRS), Hamilton Depression Scale (HDRS), Baptista Depression Scale (EBADEP-A, EBADEP-Health), Inventory of Depressive Symptomatology (IDS), Quick Inventory of Depressive Symptomatology (QIDS), Scale of Depressive Thoughts (EPD), Center for Epidemiological Studies Depression Scale (CES-D), Patient Health Questionnaire (PHQ-9), Liebowitz Social Anxiety Scale (LSAS), Hospital Anxiety and Depression Scale (HADS) , Hamilton Anxiety Scale (Ham-A), Beck Anxiety Inventory (BAI), State-Trait Anxiety Inventory (STAI), Generalized Anxiety Disorder Scale (GAD-7).
- Studies that diagnose Rheumatoid Arthritis using the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) criteria will be included.

- Studies that assess the activity of Rheumatoid Arthritis using the DAS28 score will be included.
- Studies including cyclic citrullinated peptide (CCP), rheumatoid factor (RF), ESR, CRP tests to measure Rheumatoid Arthritis activity.
- There will be no time restriction.
- There will be no language restriction.

Articles in press, protocols, abstracts without full text, letters to the editor, review articles, descriptive observational studies, book chapters or guidelines will be excluded.

2.3 Search strategy and information sources

The search will be done in the following databases: Medline/PubMed, Embase, Scopus, Web of Science, LILACS, Cochrane Library and PsycInfo. There will also be a search done in PROQUEST for thesis and dissertations.
The search strategy for PubMed is available in the following URL: https://www.crd.york.ac.uk/PROSPEROFILES/404169_STRATEGY_20230301.pdf

2.4 Data Selection and collection process

The files with the results of searches in the databases will be transferred to the RAYYAN tool for the login of 3 researchers (REVIEWER1, REVIEWER2, JUDGE), using the option of blinding among the evaluators.

The first stage will be the screening process, where the reviewers will read the title and abstract of the articles and make the decision to include or exclude them. At the end of the screening process there will be an evaluation of both reviewers to resolve any differences. The third researcher may be consulted to resolve cases in which there was no consensus. With the result of the screening, the articles will go through the eligibility phase, which will have their complete files analyzed according to the inclusion and exclusion criteria. Articles that used at least one of the RA diagnostic criteria and at least one of the anxiety and/or depression assessment tools will be grouped by similarity for inclusion in the meta-analysis.

With the result of the Eligibility Phase, the 2 evaluators will move on to the data extraction phase. At this stage, an Excel table will be generated specifically for the study and both evaluators, still blindly and independently, will fill in the columns with the respective data.

2.5 Data extraction

Data will be extracted from the following variables:

Author's name, year of publication, country, sample size, gender of the population, age, BMI, follow-up time, comorbidities: HTA, CVA, DM, CVD, chronic kidney disease, cancer, smoking packets per year, presence of depression disorder, presence of anxiety disorder, pharmaceutical treatment for depression , pharmaceutical treatment for anxiety, family history of RA, presence of RA, disease duration, RF, ACPA, DAS28, treatment, person-years, Odds-ratio (OD), Relative risk (RR) with 95% CI.

2.6 Outcomes and prioritizations

The primary outcome is the chance of developing Rheumatoid Arthritis in patients with depression and/or anxiety. The presence of RA will be considered through the ACR or EULAR criteria.

The secondary outcome is the standardized mean difference of RA in patients with depression and/or anxiety.

The presence of depression or anxiety disorder will be considered:

- Sccording to the Hospital Anxiety and Depression Scale (HADS) when the score is between 8-10 (possible) and between 11-21 (probable).

The presence of depression will be considered when results from the assessments tools indicate moderate or severe depression:

- according to the Beck Depression Inventory (BDI) when values are between 20-28 (moderate depression) and values above 28 (severe depression);
- according to the Montgomery-Asberg Depression Scale (MSDRS) when values are between 20-34 (moderate depression) or above 34 (severe depression);
- according to the Baptista Depression Scale (EBADEP-A, EBADEP-Saúde) when the values are ≥ 66 points.
- according to the Hamilton Depression Scale (HDRS) when values are between 18-24 (moderate depression),≥ 25 (severe depression);
- according to the Inventory of Depressive Symptomatology (IDS) when the values are between 26-38 (moderate depression), 39-48 (severe depression), or between 49-84 (very severe depression);
- according to the Quick Inventory of Depressive Symptomatology (QIDS-SR 16) when values are between 11-15 (moderate depression), 16-20 (severe depression), or between 21-27 (very severe depression);
- According to the Depressive Thoughts Scale (EPD) when the values are between 19-29 (moderate to severe depression), or between 30-63 (severe depression).
- According to the Depression Scale of the Center for Epidemiological Studies (CES-D) when values are ⩾23 for probable depression.
- According to the Patient Health Questionnaire (PHQ-9) when values are between 10-14 for moderate depression, between 15-19 for moderately severe depression, or 20-27 for severe depression.

The presence of anxiety will be considered when the results of the assessment tools indicate moderate or severe anxiety:

- According to the Beck Anxiety Inventory (BAI) when values are between 20-30 (moderate anxiety) or between 31-63 (severe anxiety);
- According to the Hamilton Anxiety Scale (HAM-A) when values are between 16-25 (moderate anxiety), or ≥26 severe anxiety;
- According to the Liebowitz Social Anxiety Scale (LSAS) are ≥0.79 (moderate anxiety) or ≥0.94 (high anxiety).
- According to the State-Trait Anxiety Inventory (STAI) when values are between 38-44 for moderate anxiety, or 45-80 for severe anxiety.
- According to the Generalized Anxiety Disorder Scale (GAD-7) when values are between 10-14 for moderate anxiety, or between 15-21 for severe anxiety.

2.7 Risk of bias

To assess the risk of bias in observational cohort and case-control studies, the Newcastle-Ottawa Scale will be used. A quality score will be calculated based on three categories: group selection (four items), group comparability (one item), and outcome (3 items). A maximum of one star can be awarded for each item in the categories of group selection and outcome and exposure assessment. A maximum of two stars can be awarded

for comparability. Thus, the maximum score will be nine points and will represent the highest methodological quality.

2.8 Data analysis

Randomized meta-analysis models will be used in the presence of high heterogeneity through I^2. For low heterogeneity, fixed effect models will be performed. Heterogeneity will be represented by the Baujat plots. For the analysis of categorical variables, the analysis of Relative Risk (RR) and Odds Ratio (OR) will be carried out using the Mantel-Haenzel method. For the analysis of continuous variables, the analysis of the Standardized Mean Difference (SMD) will be performed. The fixed and random estimates of the RR, OR and SMD with a Confidence Interval (CI) of 95% will be calculated separately.

For sensitivity and influence analyses, the "Leave one out" analysis will be performed, excluding one study at a time in each analysis.

If the number of studies satisfies the conditions of the method, subgroup analysis and/or meta-regression will be performed to assess the influence of clinical variables on the sum of the effect size.

If the effect sizes obtained from the studies are not sufficient to perform a meta-analysis, a narrative synthesis will be performed according to the Synthesis Without Meta-analysis (SWiM) guide (Campbell et at., 2020).

3. Discussion

We searched the main databases and the PROSPERO registry and found no systematic review that answered our research question. As far as we know, this is an unprecedented systematic review on the proposed theme. The protocol has some limitations like the different variables (comorbidities) that can modulate Rheumatoid Arthritis activity and the different psychological inventories to measure depression and anxiety that can generate some bias.

This research will be included because of a doctoral thesis, and we intend to publish this systematic review in a peer-reviewed journal. The results of this systematic review seek to fill in the knowledge gaps in this area of psychoneuroimmunology. We seek to bring information to help specialists and researchers, to have a biopsychosocial view of patients and to be able to prevent and treat psychological disorders to avoid the trigger for RA.

Acknowledgement

To the "Coordenação de Aperfeiçoamento de Pessoal de Nível Superior"(CAPES), that provides the postgraduate scholarships.

Publication

This article is unpublished and is not being considered for any other publication. The author(s) and reviewers did not report any conflict of interest during their review. Therefore, the journal Scientia Amazonia holds the copyright, has the approval and permission of the authors for the dissemination of this article by electronic means.

References

Campbell M, McKenzie J E, Sowden A, Katikireddi S V, Brennan S E, Ellis S et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline BMJ 2020; 368 :l6890 doi:10.1136/bmj.l6890

Fakra E, Marotte H. Rheumatoid arthritis and depression. Joint Bone Spine. 2021 Oct;88(5):105200. doi: 10.1016/j.jbspin.2021.105200. Epub 2021 Apr 28. PMID: 33932572.

Geenen R, Newman S, Bossema ER, Vriezekolk JE, Boelen PA. Psychological interventions for patients with rheumatic diseases and anxiety or depression. Best Pract Res Clin Rheumatol. 2012 Jun;26(3):305-19. doi: 10.1016/j.berh.2012.05.004. PMID: 22867928.

Germain V, Scherlinger M, Barnetche T, Pichon C, Balageas A, Lequen L, Shipley E, Foret J, Dublanc S, Capuron L, Schaeverbeke T; Fédération Hospitalo-Universitaire ACRONIM. Role of stress in the development of rheumatoid arthritis: a case-control study. Rheumatology (Oxford). 2021 Feb 1;60(2):629-637. doi: 10.1093/rheumatology/keaa216. PMID: 32533144.

Lu MC, Guo HR, Lin MC, Livneh H, Lai NS, Tsai TY. Bidirectional associations between rheumatoid arthritis and depression: a nationwide longitudinal study. Sci Rep. 2016 Feb 9;6:20647. doi: 10.1038/srep20647. PMID: 26857028; PMCID: PMC4746638.

Marrie RA, Walld R, Bolton JM, Sareen J, Walker JR, Patten SB, Singer A, Lix LM, Hitchon CA, El-Gabalawy R, Katz A, Fisk JD, Bernstein CN; CIHR Team in Defining the Burden and Managing the Effects of Psychiatric Comorbidity in Chronic Immunoinflammatory Disease. Rising incidence of psychiatric disorders before diagnosis of immune-mediated inflammatory disease. Epidemiol Psychiatr Sci. 2019 Jun;28(3):333-342. doi: 10.1017/S2045796017000579. Epub 2017 Nov 3. PMID: 29098977; PMCID: PMC6998907.

Nerurkar L, Siebert S, McInnes IB, Cavanagh J. Rheumatoid arthritis and depression: an inflammatory perspective. Lancet Psychiatry. 2019 Feb;6(2):164-173. doi: 10.1016/S2215-0366(18)30255-4. Epub 2018 Oct 23. PMID: 30366684.

Pan W, Stone KP, Hsuchou H, Manda VK, Zhang Y, Kastin AJ. Cytokine signaling modulates blood-brain barrier function. Curr Pharm Des 2011; 17: 3729–40.

Radu AF, Bungau SG. Management of Rheumatoid Arthritis: An Overview. Cells. 2021 Oct 23;10(11):2857. doi: 10.3390/cells10112857. PMID: 34831081; PMCID: PMC8616326.

Schiltz JC, Sawchenko PE. Distinct brain vascular cell types manifest inducible cyclooxygenase expression as a function of the strength and nature of immune insults. J Neurosci 2002; 22: 5606–18.

Skinner-Taylor CM, Perez-Barbosa L, Corral-Trujillo ME, Perez-Onofre I, Barriga-Maldonado ES, Cardenas-de la Garza JA, Riega-Torres J, Galarza-Delgado DA. Anxiety and depression in reproductive age women with rheumatic diseases. Rheumatol Int. 2020 Sep;40(9):1433-1438. doi: 10.1007/s00296-020-04591-8. Epub 2020 May 5. PMID: 32372140.

Song H, Fang F, Tomasson G, et al. Association of Stress-Related Disorders With Subsequent Autoimmune Disease. *JAMA.* 2018;319(23):2388–2400. doi:10.1001/jama.2018.7028

Sparks JA, Malspeis S, Hahn J, Wang J, Roberts AL, Kubzansky LD, Costenbader KH. Depression and Subsequent Risk for Incident Rheumatoid Arthritis Among Women. Arthritis Care Res (Hoboken). 2021 Jan;73(1):78-89. doi: 10.1002/acr.24441. PMID: 32937012; PMCID: PMC7775283.

Vallerand IA, Lewinson RT, Frolkis AD, Lowerison MW, Kaplan GG, Swain MG, Bulloch AGM, Patten SB, Barnabe C. Depression as a risk factor for the development of rheumatoid arthritis: a population-based cohort study. RMD Open. 2018 Jul 11;4(2):e000670. doi: 10.1136/rmdopen-2018-000670. PMID: 30018804; PMCID: PMC6045711.

Vallerand IA, Patten SB, Barnabe C. Depression and the risk of rheumatoid arthritis. Curr Opin Rheumatol. 2019 May;31(3):279-284. doi: 10.1097/BOR.0000000000000597. PMID: 30789849; PMCID: PMC6455087.

***Scientia Amazonia*, v. 12, n.2, B18-B25, 2023**
Revista on-line http://www.scientia-amazonia.org
https://doi.org/10.5281/zenodo.8317183 -ISSN:2238.1910