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Comorbidity of Depression and Rheumatoid Arthritis – A Literature Review

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ABSTRACT

Introduction and purpose

Rheumatoid arthritis is a chronic inflammatory disease affecting joints, heart, kidneys, and lungs. It is often bilaterally associated with depression, presenting with sleep troubles, fatigue, and chronic pain, inevitably leading to disability and significant worsening of patients' quality of life. This review aims to summarize the current knowledge on the comorbidity of RA and depression, exploring shared etiological factors, challenges in research methodology, and therapeutic approaches.

A brief description of the state of knowledge

Inflammatory mechanisms, including elevated plasma levels of pro-inflammatory cytokines, play a crucial role in both conditions. Biological treatments have shown promise in alleviating depressive symptoms in treatment-resistant depression (TRD). Cognitive behavioral therapy (CBT) and pharmacotherapy, including serotonin-norepinephrine reuptake inhibitors (SNRIs), have proven effective in managing depression in RA patients. In general, it worsens their condition and accelerates disability.

Conclusions

The comorbidity of RA and depression is the most significant among all mental diseases. Despite known etiology, further studies should focus on standardized methodology, unification of diagnostic criteria, full representation of all social groups, as well as further research on biological drugs and their effectiveness in depression and RA not only as comorbidities, but also separate diseases.

Keywords: Rheumatoid arthritis, depression, comorbidity, chronic inflammation

1. Introduction and purpose

Rheumatoid arthritis (RA) is an inflammatory disorder. It affects not only joints, but also the cardiovascular system, pulmonary system, kidneys and many more. [1,2,3] Higher prevalence in the women population is observed, with male-to-female ratio 3:1. [4,7] A pharmacological treatment is burdened with many side effects. Symptoms such as chronic pain, fatigue, troubles with sleep, perspective of chronic disease with limited options of cure, loss of social roles, and deformations of joints are all inevitably leading to disability. [5] Another illness significantly worsening the quality of life is depression. It is the second leading cause of year loss due to disability. [6] In the general population, female sex is associated with an increased prevalence of depression and anxiety globally. [7] Depression, if left untreated, leads to death by suicide. These two morbidities often coexist and linking between them seems to be bilateral.
The aim of this work is to summarize and share available knowledge about rheumatoid arthritis and depression comorbidity, their shared etiology, challenges in research methodology, and options of the most effective treatment.

2. Description of the state of knowledge

General information

In the population-based cohort in Manitoba, Canada the incidence rate ratio (IRR) of depression was significantly increased in RA patients population in comparison to the general one. Some sources say that 30% of patients suffering from RA will develop depression within 5 years of basis diagnosis. [7, 14] On the other hand, in the Taiwanese research (one of the first investigating the risk of RA in depression) the incidence of RA in the depressed population was higher (65%) compared to the rate in the non-depressed one. This risk was increased in a group of patients younger than 40 years old. The longer a patient suffers from depression, the higher incidence of RA is observed. However, mechanism why depression can induce RA remains unclear. [8, 11] Any psychiatric comorbidity, especially depression at onset of RA worsens pain and reduces chances for positive response for treatment in the first year by 40%. [9] The link between other mental illnesses such as schizophrenia or bipolar disorder has not been proven. [10] However, some genetic loci are associated with the risk of RA and other immune-mediated disorders. [11]

Common proinflammatory theory of rheumatoid arthritis and depression and role of biological treatment

The precise pathophysiology of depression is yet to be fully understood, nevertheless one of the theories indicates inflammation as a cause. [12] The presence of high plasma levels of C-reactive protein (CRP) has been linked with depression resistance for treatment. Additionally, elevated levels of pro-inflammatory cytokines, such as IL-1, IL-6, IL-18, and tumor necrosis factor (TNF), are frequently observed in depression. These are factors characteristic for autoimmune diseases such as RA, but unexpectedly elevated plasma levels of cytokines can be observed in depression even in the absence of autoimmune disease. Elevated pro-inflammatory cytokines are linked to reduced levels of anti-inflammatory cytokines such as IL-10, potentially exacerbating depressive symptoms. Additionally, higher levels of pro-inflammatory markers are associated with poorer treatment outcomes, regarding depression resistance for treatment and anti-inflammatory agents, including N-acetylcysteine and minocycline showed potential in treating. An anti-TNF agent, infliximab has demonstrated promise in alleviating depressive symptoms, with studies indicating that it can reduce depression severity by approximately 50% in patients with TRD. These findings are crucial, because RA is an effect of upregulation of IL-1, IL-6, IL-18, and tumor necrosis factor (TNF) and one of the medications used in RA treatment is infliximab. The mechanism how RA induces depression is well-established. However, the reverse—how depression may trigger RA—remains unclear. Depression in RA seems to be driven by immunological changes and is not simply a result of chronic pain, disability, or fatigue. A significant correlation was found between the plasma levels of IL-1 receptor antagonist (IL-1RA) and the severity of depressive symptoms, such as loss of appetite, anhedonia, and sleep disturbances. Higher plasma concentrations of TNF are associated with anxiety, and anti-TNF therapies mentioned before showed reduction of anxiety symptoms in RA patients. While evidence supporting TNF's role in depression is robust, the use of anti-TNF therapies in depression remains insufficiently explored. Clinical trials targeting IL-6 (another pro-inflammatory cytokine), such as those investigating the efficacy of sirukumab and tocilizumab, have shown mixed results, with some studies failing to demonstrate significant improvements in depression symptoms. However, given the growing evidence of inflammatory cytokines' involvement in depression, there is continued interest in developing cytokine-targeted therapies as adjuncts to traditional antidepressant treatments

Although plasma levels of pro-inflammatory cytokines can remain normal, there are studies showing their elevated levels in cerebrospinal fluid (CSF). Two mechanisms why peripheral cytokines can affect brain functions are distinguished. First is via the neural pathway, where pro-inflammatory cytokines activate primary afferent nerves, such as the vagus nerve. Subsequently brain nuclei, including amygdala - a key structure involved in emotional regulation- are modulated. Second one is via the humoral pathway, where cytokines and pathogen-associated molecular patterns (PAMPs) directly interact with the choroid plexus and circumventricular organs, bypassing the blood-brain barrier. These activated structures trigger the release of additional pro-inflammatory cytokines, such as TNF, into the brain, further promoting inflammation within the CNS. Once these cytokines reach the brain, they have an impact on neurotransmitter systems, particularly serotonin, by reducing tryptophan availability via upregulation of the enzyme indoleamine 2,3-dioxygenase (IDO). TNF can also increase the expression of the serotonin transporter, lowering the level of available serotonin in neurotransmitter systems. Additionally, pro-inflammatory cytokines elevated glutamate levels, with neurotoxic effects resulting from the increased production of kynurenine, which is converted into glutamate. These inflammatory processes impair neurogenesis and neuroplasticity, reducing the expression of brain-derived neurotrophic factor (BDNF), a critical mediator of neuronal health. Cytokines also alter the function of the hypothalamic-pituitary-adrenal (HPA) axis, a central system in the regulation of stress and mood. Its dysregulation leads to increased systemic inflammation and potentially triggering conditions such as RA. [11, 13, 14, 21, 23]

Psychotherapy and pharmacological treatment of depression in RA context

The prevalence of depression is higher among RA patients compared to those with other chronic conditions, such as Parkinson's disease, diabetes mellitus (DM), or the general population without chronic physical illness. [16, 17] Individuals with depression are less likely to adhere to prescribed medications, experience more frequent pain, and make more medical visits. [18,19,20] Moreover, depressed individuals are more likely to smoke, which is a known pro-inflammatory factor that further exacerbates RA symptoms. Smoking is also a well-established risk factor for RA, and it is also a significant contributor to the development of depressive disorders. The inflammatory effects of smoking are linked to increased oxidative stress and alterations in both the immune system and epigenetic factors. Smoking cessation has been

associated with improvements in depressive symptoms, while continued smoking negatively impacts RA outcomes, including increased pain intensity and prolonged morning stiffness in RA patients. [21, 22, 23, 24, 25] Depression is associated with higher levels of anxiety, which affects approximately 13-70% of RA patients, with prevalence being highest in the first year following diagnosis. [7, 26, 27, 28] This may be attributed to the stress response and the inability to effectively cope with the new disease burden. Cognitive behavioral therapy (CBT) has proven effective in alleviating both depressive and anxiety symptoms in RA patients, with the cognitive component of therapy appearing to be more influential than the behavioral aspect. Key factors contributing to the effectiveness of CBT include self-esteem and coping abilities. In terms of pharmacological treatment, serotonin-norepinephrine reuptake inhibitors (SNRIs) have been found to be more effective than selective serotonin reuptake inhibitors (SSRIs) in treating depression in RA patients. Tricyclic antidepressants also seem to be effective. Interestingly, the use of antidepressants may also have a protective effect on the development of RA, possibly due to their direct anti-inflammatory effects.[29] However, despite advancements in the treatment of major depressive disorder (MDD), it is estimated that approximately 50% of patients do not respond to initial treatment regimens, and 15-30% of individuals remain treatment-resistant, even with pharmacotherapy or psychotherapy. [14, 30, 31] A population-based study using data from The Health Improvement Network (THIN) cohort analyzed the risk of incident RA in individuals with MDD compared to the general population. The risk of RA was significantly lower in individuals with MDD who used antidepressants, suggesting a potential protective effect of antidepressant use against the development of RA. [14, 32, 33] The biological mechanisms linking stressful life events to RA development may, in part, be mediated through MDD. Studies examining the impact of post-traumatic stress disorder (PTSD) on RA risk have demonstrated that individuals with PTSD symptoms have an increased likelihood of developing RA. For example, data from the Nurses' Health Study showed that individuals with at least four PTSD symptoms had a 76% increased risk of developing RA. [34]

Suicide in RA

Suicidal thoughts and are among the most common psychiatric symptoms affecting patients with RA. The most severe consequence of depression is suicide. In population of patients suffering from RA suicide is committed more often by women (52,6%). In comparison, in 2023

in polish society men made up approximately 84% of suicide attempts ended by death. However, women are more likely to attempt. This difference may be caused by a higher percentage of women suffering from RA. Additionally, another risk factor of depression is old age, and RA is very common in the population of elderly people- the disease usually begins in the fourth decade of life. It is worth to mention method of suicide among women with RA is violent in most cases. However, in a study using administrative data from Manitoba, Canada, depression was associated with increased mortality (attributable proportion 6.9%). Suicide rates and attempts were considered in this analysis; however, RA-specific estimates with depression and suicide were not statistically significant. [4, 7, 35]

Troubles in research

The incidence and prevalence of psychiatric disorders in RA are incompletely understood. Sources report that the percentage of RA patients suffering from depression ranges from 0.04% to 66.3%. The most common types are major depression (16.8%) and dysthymia (18,7%). This wide discrepancy is caused by some factors. Firstly, symptoms such as fatigue and sleep disturbances are common for both depression and RA. This complicates the differentiation of the two conditions, making it challenging to ascertain the precise cause of these symptoms. Secondly, studies using only self-reported questionnaires examining moods may overestimate the prevalence of depression, as they do not account for the complexities of mood disorders in RA patients. Another complicating factor is the inconsistent definition of depression across studies, which makes standardizations hard. Additionally, many prior studies examining the prevalence of depression or anxiety in RA have been of low quality due to methodological issues such as non-population-based sampling, low response rates, and small sample sizes. Classic depression questionnaires such as Beck Depression Inventory for Primary Care or Hospital Anxiety and Depression Scale are designed to identify depression in primary care patients. As a result, they tend to eliminate the somatic components of depression. Usefulness of the Patient Health Questionnaire-9 (PHQ-9) and the Geriatric Depression Scale (GDS) in older patients was proven. Furthermore, individuals from lower socioeconomic status (SES) populations appear to be underrepresented in RA-related research, despite being more vulnerable to depression. Finally, the scale thresholds used to identify depression are not unified. [7, 14, 20, 36, 37, 38, 39, 40, 41]

2. Conclusions

To conclude, the link between RA and depression is indisputable. Regarding their common inflammatory etiology further research ought to focus on biological treatment. It has been proven that depression can increase the risk of another inflammatory arthropathy, psoriatic arthritis, inflammatory bowel disease, alopecia areata, and vitiligo. It is essential to remember that depression is a risk factor of cognitive impairment and causes negative perception of a man as an individual and future. In consequence, poorer effects of treatment may be expected. Another fundamental aim is to create questionnaires that would precisely diagnose depression in RA and would be available for all social groups with special attention paid to those characterized by lower financial status.

Disclosure:

Author's contribution:

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Software: Aleksandra Galanty-Ochyra, Jan Węgrzyn
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