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## Depression, A Mental Aspect in Rheumatoid Arthritis Comorbidities

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### ABSTRACT

Rheumatoid arthritis (RA) significantly impacts patients' mental health, especially in generating depression. It is affected by RA clinical presentations of deformities, pain, and disability that significantly affect patient quality of life and become a stressor to mental comorbidities. Clinicians and society often overlook mental issues related to a disease, including patients and their families. Mental issues, especially depression, have become a global burden for people of all ages. This review presents the recent study of depression as a comorbid to rheumatoid arthritis patients. Recent studies correlate depression with increased RA progressivity that is mediated by inflammation mechanisms. Through this mechanism, the RA progressivity affects the occurrence of depression, but also, the depression worsens the RA symptoms. Although most RA therapy help reducing depression, a few do the opposite. Some of the assessment has been developed in helping clinicians evaluate RA disease activity and depression early. The understanding and awareness of the bidirectional mechanism will help clinicians improve the management of rheumatoid arthritis and depression.

### 1. Introduction

Rheumatoid arthritis is a long-term systemic disease.<sup>1,2</sup> It produces chronic pain, deformities, and a certain degree of physical disabilities and affects mental health, such as depression.<sup>3,4</sup> The RA disability interferes with patients' daily function and activity that will lead to depression. Pro-inflammatory cytokines in RA can also trigger depression; increasing pro-inflammatory cytokines will trigger the activation of the hypothalamic-pituitary-adrenal (HPA) axis.<sup>1,2,4-6</sup> Clinicians and society often overlook mental issues related to a disease, including patients and their families. Mental issues, especially depression, have become a global burden for people of all ages.<sup>5,7</sup> The author would like to raise the awareness of depression posed by chronic pain-related-disease such as rheumatoid arthritis and the pathogenesis of this interaction.

#### Rheumatoid arthritis

Rheumatoid arthritis (RA) generates synovial inflammation that causes progressive destruction of the articular cartilage and deformities.<sup>6,8</sup> RA is one of the most common autoimmune diseases with joint involvement.<sup>3,4</sup> Rheumatoid arthritis occurs in 0.5 to 1% of the population around the world, covering all ages and 3-4 times more dominant in women.<sup>2,6,8</sup> RA primarily targets joints causing polyarthritis. It happens on both sides of the body (symmetric). The inflammation is not only in small joints of the hand and foot (causing swan-neck deformity in late-stage) but also in other parts of the body, such as eye (scleritis), lung (interstitial fibrosis), and blood vessels (vasculitis).<sup>4,9</sup> Cardiovascular disease, osteoporosis, and fibromyalgia are significant comorbidities, while lymphoma is a potentially fatal consequence of the

illness<sup>2,3,9</sup>

Pathogenesis is a complicated process that includes the interplay of genes and the environment.<sup>4</sup> Possible mechanism of the triggers is by carbamylation, acetylation or, the citrullination of arginine in matrix protein. The proteins turn into antigens, subsequently given to T cells in triggering the activation of B cells to produce antibodies. Antibodies, pro-inflammatory cytokines, and chemokines in the bloodstream can be found ten years before the symptoms.<sup>2,5,7,9</sup>

Synovitis appears to be caused by anti-citrulline and antibodies, such as Rheumatoid Factor, destructing microvascular, activating complement, and generating immune complexes in conjunction.<sup>9</sup> Autoantibodies to IgG and citrullinated proteins develop in most patients with RA, while others do not. This variability affects RA symptoms and progressivity. Genetic and environmental variables interact in creating synovial inflammatory and damaging reaction in people with a predisposing genotype. The definite explanation is still unknown.<sup>4</sup> The research about the triggers such as dental problems, hazardous dust, and smoke exposure is still in its early stages.<sup>9</sup>

Untreated RA frequently leads to joint deterioration that worsens over time, resulting in permanent disability. Recent RA therapies are the study result that has elucidated some of the basic mechanisms that underpin the onset and development of autoimmunity. DMARDs (disease-modifying anti-rheumatic medications) and NSAIDs are often taken with or without steroids. DMARDs are currently classified as either synthetic or biologic. Original biologic and biosimilar DMARDs are two types of biologic DMARDs. Sulfasalazine, methotrexate, and antimalaria are examples of non-specific immunosuppressive synthetic DMARD.<sup>9</sup> When needed, clinicians may continue using biologic DMARD (IL-6 dan TNF $\alpha$  inhibitor, rituximab).<sup>4,9</sup> Nowadays, targeted synthetic DMARD is being created. An example is Tofacitinib that successfully controls RA progression by promoting drug-dependent remission. RA is not incurable anymore.<sup>2,9</sup>

### **Depression in RA**

Depression is a common mental disorder, ranging from 1.5 to 19 cases per 1000 adult population.<sup>6</sup> Depression ranks as the third global burden.<sup>7</sup> The etiology of depression is not fully understood—the key factors, including inflammatory reactions and associated immunological disturbances involving the central nervous system. Depression often accompanies 20-30% of AR patients or 2-4 times from normal society after the first-five-year diagnosis.<sup>1,2,4,9-11</sup> As the disease progresses, the mental problem in patients with rheumatoid arthritis may elevate depression risk, and the deformities, accompanying pain, and impairments in RA patients may cause depression. The relationship between depression and RA was proportionately related to the amount of pain reported by patients. At a certain point, RA can make someone become jobless and limit their working activity, contributing to shunning and depression. More significant RA comorbidities may affect depression.<sup>1,6,9</sup>

The prominent risk of depressed arthritis patients was explained by the HPA axis malfunction and the quantity of peripheral glucocorticoid, which increased the tendency of autoimmune disturbance and rheumatoid arthritis.<sup>6,7</sup> The mechanism of systemic inflammation points to a two-way relationship between RA and depression by increasing pain and worsening disease activity and patients' response to medication without elucidating the mechanism.<sup>2,5,6,10</sup> People suffering from depression may have poorer adherence rates, and physiological changes linked with depression may compromise drug effectiveness, reducing RA remission.<sup>2,3</sup>

In RA, systemic inflammation may lead to a higher risk of depression. Many pro-inflammatory markers linked with rheumatoid arthritis, such as IL-1b, IL-6, TNF- $\alpha$ , IL-18 and others, are often related to inflamed brain neural in depression.<sup>2,4,5,7</sup> There is proven interaction between peripheral and brain inflammatory pathways.<sup>2,10</sup> Displacing peripheral inflammatory substances to the brain through the endothelial cell of the blood-brain barrier and altered

efflux transporters may cause neural inflammation. Pro-inflammatory cytokines are thought to stimulate tryptophan and serotonin-degrading enzymes in the humoral system while increasing the synthesis of glutamatergic NMDA receptor agonists, resulting in serotonin shortage and glutamate overproduction, resulting in depression.<sup>3,6</sup>

Furthermore, inflammatory factors reduce neurotrophin and brain-derived neurotrophic factors, which affect neuroplasticity and neurogenesis. **Lwin** There might be additional possible links between RA and depression than pro-inflammatory variables and systemic inflammation. Vitamin D deficiency in patients with rheumatoid arthritis has been proposed as a potential predictor of depression.<sup>3</sup> Individual coping styles can impact how RA patients manage their condition successfully.<sup>2,9</sup> RA manifestation also hamper patients' attempt to cope and adapt efficiently due to various ways to adapt in living with RA. Active coping methods, for example, enhance psychological and physical well-being in people with RA (such as physical workout, problem-solving, reassessment of impractical and negative beliefs).<sup>9</sup> A passive approach such as shunning, on the other hand, harms health and adaptability.<sup>2,9</sup>

Disastrous cognitions are more prevalent in RA patients than in healthy people, and they are linked to increased inflammation, discomfort, and particular need.<sup>9</sup> In a recent study evaluating the impact of csDMARDs and bDMARDs on psychological manifestation in rheumatoid arthritis, biologics were found to have few substantial impacts on psychological health. Nevertheless, some research missed the quality-of-life assessment. It is also worth noting that pharmacologic studies typically exclude individuals with significant affect disorders and have inadequate psychometric tools for measuring depression.<sup>2,4,9</sup>

A multifaceted approach is utilized to assess remission in the treatment of RA. Disease activity (DAS28, CDAI, and SDAI), disability (HAQ-DI), pain (VAS), quality of life (e.g., Euro QoL Five Dimensions or EQ5D), and depression (BDI II, HAMD, SF36 MH,

DASS, and HADS) are all assessed in RA patients.<sup>2,3,8</sup> A total of 28 joint exams were used to score disease activity in people with RA. Examination of the swollen and tender joint, pain score, questionnaires, and imaging are all used to assess disease activity in RA. The Clinical Disease Activity Index (CDAI) and the Simplified Disease Activity Index (SDAI) are two more ways to assess RA disease activity in more straightforward and more comprehensible approaches that can be used anytime and anywhere.<sup>2</sup> Health Assessment Questionnaire-Disability Index (HAQ-DI) evaluates disability assessment responsive to change in disease activity. A general pain score evaluation with the Visual Analog Scale (VAS) describes pain quality in numbers 1 to 10.<sup>8</sup> Depression alone can be measured with Beck Depression Inventory-II (BDI-II) and Hamilton Depression Rating Scale (HAM-D) or can be assessed with other mental problems by using Short Form 36 for Mental Health (SF36 MH), The Depression, Anxiety and Stress Scale (DASS), and Hospital Anxiety and Depression Scale (HADS).<sup>2</sup>

### **Rheumatoid arthritis therapies impact on depression**

Recent data about increasing inflammation in depression bring interest in targeted anti-cytokine therapy as the primary management of depression. RA treatment with DMARD has shown improving depression and other mental disorders. Studies have shown that csDMARDs such as sulfasalazine, methotrexate, and leflunomide improve body pain, mental impairment, and RA patient quality of life by measuring SF36 and HAQ-DI. An improvement in HAQ-DI in 3 months is seen in RA patients treated with leflunomide. bDMARD such as tocilizumab inhibits IL-6, which later also inhibits JAK kinase, which decreases depression impact.<sup>3,5</sup> This JAK inhibition is similar to some antidepressant mechanisms.<sup>2,5,10</sup> 12-month therapy with infliximab resulted in depression remission (as measured by HAM-D) in young female RA patients and a 50% reduction in depressed symptoms via glucose and lipid regulation. tsDMARD such as tofacitinib shows an

excellent reduction in pain, improving RA patients' quality of life, thus reducing depression risk in RA patients.<sup>2,4</sup>

Aside from DMARDs, NSAIDs and glucocorticoids are used as a first-choice drug in improving RA symptoms.<sup>4</sup> Celecoxib, a COX-2 inhibitor, shows a reducing depression in a mouse model in comparison to fluoxetine.<sup>9</sup> When other treatments for RA diminish depression, glucocorticoids do the opposite. The glucocorticoid receptor is essential for the proper functioning of the HPA axis, which is accountable for depression.<sup>6,7</sup> Prednisolone was found to produce similar depressed behavior in the animal model investigation.<sup>2</sup>

Besides pharmacology therapies, scientific evidence of nutritional improvement as a lifestyle modification for psychological disorders in the general community has risen. Fish, fruits, and vegetables have been proven to alleviate depression. These foods include various minerals suitable for depression (Ca, Mg, Fe, vitamin C, and folic acid), including n-3 polyunsaturated fatty acids (PUFAs). Furthermore, because many of these foods and minerals are well-known for their anti-inflammatory properties in various illnesses related to RA, they may be predicted to have positive impacts on mental health and RA disease activity.<sup>3</sup>

The study by Minamino et al. is the pioneer to show the relationship between depression and particular food preferences in a RA. Patients with a higher HADS depression score show higher scores in HAQ-DI and DAS28-CRP assessments. These findings support other recent research that shows depression interacts with RA inflammation and significantly impacts disease outcomes. The HADS depression level was negatively linked to higher fruit, fish, and vegetable consumption, daily function, and the usage of methotrexate. These findings support earlier finding that depression lowers the probability of RA remission, and methotrexate may help with psychological disorders, RA progressivity, and HAQ.<sup>3</sup>

A growing body of data suggests that specific nutrient and diet patterns are involved in forming or

preventing mental illnesses in the community. A meta-analysis found that eating more fish, fruits, whole grains, and vegetables is linked to a lower risk of depression, but eating more processed foods, sweets, and saturated fats may raise depression. Furthermore, newer studies have demonstrated that such balanced diets reduce clinical depression in young and middle-aged individuals. Moreover, fish-derived omega-3 consumption and the omega-6 and -3 ratio of plasma polyunsaturated fatty acid are negatively related to depression. Potential studies in Japan found that frequent fish consumption or its omega-3 is substantially linked to a lower risk of depression over time. Particular food choices may have positive impacts on mental anguish in RA patients. However, based on these findings, the long-term effect of eating patterns is barely known and therefore needs further investigation. As proven in clinical publications, several recommended diets for depression, such as omega-3 rich-fish, fruits, and vegetables, are also famous for their anti-inflammatory benefits against RA. Food combining appears to be a promising co-adjuvant treatment for RA patients with mental illnesses.<sup>3</sup>

## 2. Conclusion

Data suggest that depression has a more significant impact on the patient than what we initially believed. It not only causes depression, it turns out that RA is also exacerbated by depression, as reported in recent studies. The inflammation theory in depression reveals one possible mechanism through which depression raises RA risk by promoting exacerbation and reducing remission.<sup>3</sup> Because depression raises RA risk, patients with RA possibly have a higher risk of getting depression, which will affect compliance to therapy and their life quality.

**Lwin** Because of the subjectivity and personal negativity, depression may be more significant than the disease itself in determining patients' life quality.<sup>5</sup> Clinicians need to be aware of RA development in depressed patients since this individual may have a more significant pain-related complaint. <sup>9</sup> Knowing

this two-way correlation of rheumatoid arthritis and depression may be a good step in averting worse prognoses in each patient category. These findings have an immediate effect on the treatment option. Notably, improved depression outcomes in rheumatoid arthritis patients may result in better outcomes. Finally, when needed, physicians participating in the RA or depression treatment must assist in referring patients to the expert. Many parties must work together more effectively to implement this complete strategy. This review presents recent theory that may give a better understanding of rheumatoid arthritis, depression and its potential preventive measures.

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