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OPEN ACCESS REVIEW

Review on the Role of Estrogen Hormone in Rheumatoid Arthritis Disease

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ABSTRACT

Estrogen, a key hormone primarily involved in the regulation of the female reproductive system, has been studied for its impact on autoimmune diseases, including rheumatoid arthritis (RA). Rheumatoid arthritis is a chronic inflammatory disease that predominantly affects women, especially during their reproductive years and postmenopausal stage. Rheumatoid arthritis is an autoimmune disease in which the immune system attacks the synovial membrane of joint and produces self-antibodies like anti-citrullinated protein antibody (ACPA) and rheumatoid factors (RF). Estrogen can transiently suppress pro-inflammatory cytokines, leading to temporary improvement in rheumatoid arthritis symptoms during pregnancy or periods of high estrogen levels. When estrogen levels drop after menopause, it can exacerbate joint inflammation and degeneration, making illness more severe. The relationship between estrogen and rheumatoid arthritis diseases is complex in both immune-modulatory and inflammatory pathways. Estrogen plays an important role in controlling pro-inflammatory effects, especially during hormonal changes. It also has a role in the severity of the disease, and this varies according to the stage of the disease and the hormonal status. This study reviewed previous studies on the relationship between estrogen and rheumatoid arthritis diseases, which numbered 22 studies over different years, which demonstrated the effective role of the hormone estrogen with the body's immunity when infected with diseases in general, and rheumatoid arthritis diseases in particular. Understanding the interaction between estrogen and rheumatoid arthritis can provide insights into new treatment strategies, including hormone replacement therapy and selective estrogen receptor modulators. Extensive research is recommended to clarify the exact role of estrogen in the development and treatment of rheumatoid arthritis.

Keywords: Estrogen, immune system, Rheumatoid Arthritis, rheumatoid factors, anti-citrullinated protein antibody.

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INTRODUCTION

Overview of Rheumatoid Arthritis

Rheumatoid arthritis is a systemic inflammation chronic autoimmune disease that affect the synovial membrane of joints causing pain and swelling (1). Rheumatoid arthritis is known to have symptoms that come and go, contributing to varying symptoms over time (1). The disease mechanism of RA involves a complex interplay between genetic, environmental, and immune system factors. The major mechanisms involved in the pathogenesis of rheumatoid arthritis include:

1. Genetic Factors and RA

The presence of specific alleles of the HLA-DRB1 gene which encodes a component of the MHC II molecule in RA patients is regarded the strongest genetic risk factors for this disease, developing rheumatoid arthritis may be occur due to some variants of the HLA-DRB1 gene by altering antigen presentation to T cells (2).

2. Environmental Triggers

Infections: Various infections, particularly respiratory or periodontal infections, have been proposed as environmental triggers for RA. The bacterium Porphyromonas gingivalis (which is found in the mouth and linked to periodontal disease) can express peptidyl arginine deiminase (PAD), an enzyme that can citrullinate proteins, a process that is implicated in RA pathogenesis. Previous study found that smoking combined with exposure to P. gingivalis may increase the risk of RA through the formation of citrullinated peptides (3).

Smoking:

Smoking is a well-established environmental risk factor for RA, particularly in individuals who are genetically predisposed. Smoking promotes the formation of citrullinated proteins in the lungs, which can trigger an autoimmune response. Previous study demonstrated that smoking significantly increases the risk of RA in individuals with the shared epitope of HLA-DRB1(4).

3. Immune System Dysregulation

Loss of Tolerance: RA is considered an autoimmune disease where the immune system loses tolerance to self-antigens, particularly in the synovial joints. In RA, autoantibodies like rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) are produced and contribute to the disease process (5).

Citrulline and ACPA:

Citrulline is a post-translational modification of proteins, which is thought to play a critical role RA. *P. gingivalis* and other factors can increase the citrullination of proteins such as vimentin, collagen, and fibrinogen. These citrullinated proteins are recognized as foreign by the immune system, which results in the production of ACPAs. Previous study showed that ACPAs are specific biomarkers of rheumatoid arthritis and correlate with disease severity (5).

4. Auto-antibodies in RA

Rheumatoid factor is found in approximately 70-80% of patients with rheumatoid arthritis, and it is considered one of the hallmarks of the disease. It is an antibody directed against the Fc region of immunoglobulin G (IgG), which plays a role in the formation of immune complexes that contribute to synovial inflammation (6). Anti-citrullinated antibodies are more specific to rheumatoid arthritis and are detected before the clinical manifestation of the disease as a previous study showed that anti-citrullinated antibodies can bind to citrullinated proteins in synovial joints, leading to local inflammation and joint damage (7).

5. Inflammation and Synovial Tissue Involvement

Immune cells play an important role in the development of rheumatoid arthritis by activating synovial macrophages, dendritic cells, and T cells, which lead to the activation of T helper cells 1 (Th1) and T helper cells 17 (Th17), which in turn lead to the production of some types of pro-inflammatory cytokines such as interferon gamma (IFN-γ) and interleukin 17 (IL-17), which contribute to the destruction of cartilage and bone in the joints(8). Some cytokines such as TNF-α and IL-6 play a role in the development of rheumatoid arthritis (9).

6. Synovial Fibroblasts and Cartilage Degradation

A previous study discussed the role of activated fibroblasts that release matrix metalloproteinases and other enzymes that degrade the extracellular

matrix (10) , Cartilage components such as collagen and aggrecan may be degraded by matrix metalloproteinases (MMPs) and aggrecanases, the release of which is stimulated by some cytokines such as TNF-α and IL-1. A previous study has shown that matrix metalloproteinases are important mediators of cartilage destruction in RA (11).

7. Osseous Erosion

Previous studies have shown that inflammatory cytokines, such as RANKL (receptors activators for nuclear factor kappa-B ligand), which are usually activated in synovial membrane inflammation, promote to bone loss by activating osteoclasts (12). this study also found that RANKL promotes the development of osteoclast precursors into maturing osteoclasts by connecting to the receptors (12). Furthermore, research has shown that mediators of inflammation including TNF-α and IL-6 contribute to the upregulation of RANKL in RA, leading to increased bone losing and joint deterioration (13).

Pathophysiological for Rheumatoid Arthritis

In rheumatoid arthritis (RA), an auto-immune illness, the immune system attacks the joint synovial joints membrane and produces self-antibodies like anti-citrullinated protein antibody (ACPA) and rheumatoid factors (RF). These autoantibodies are crucial in the responses to auto-immune diseases (14). Previously research efforts have shown that cytokines, particularly IL-6 and IL-1β, play a role in the development of RA. They stimulate immune system cells, including macrophages and T cells, which in turn sustain the irritation process and lead to joints destruction (15). Joint pain, swelling, and limited range of motion are symptoms of rheumatoid arthritis, which mostly affects the small bones of the hands, fingers, and feet (16). Pulmonary disease, heart problems, and anemia are among systemic effects that could emerge (17).

Role of estrogen in the development of rheumatoid arthritis

1. Beginning

Primarily produced in the ovary, with additional synthesis occurring in the adrenal glands and adipose tissue, the hormone estrogen is the principal reproductive hormone that has far-reaching effects on the development and operation of the female reproductive system (18). The pathophysiology of RA is influenced by estrogen hormone, which controls the immune response and the way the body reacts to inflammatory stimuli. By enhancing the activation of helper T cells (Th), it influences both forms of immunity and, in turn, triggers the production of cytokines like TNF-α and IL-6, which play crucial roles in the inflammatory process linked to RA (19). In rheumatoid arthritis, inflammation-related responses are initiated and maintained by immune system cell types such dendritic cells and macrophages, whose activity is regulated by the hormone estrogen. Acknowledged for its roles in inflammatory and autoimmune diseases, this hormone promotes the formation of Th1 and Th17 T cells. An important component of RA, Th17 T cells induce neutrophil migration to the synovial cavity (20). estrogen enhances the secretion of cytokines including TNF-α, IL-1β, and IL-6, which amplify the activation of osteoclasts and exacerbate the joint degeneration commonly seen in the disease (14).

2. Sex-Based Disparities in Rheumatoid Arthritis

Previous research has shown that men are less likely to get RA than women. The impact of estrogen for the immune system was associated with gender differences; for example, women are more likely to suffer from autoimmune diseases when they are pregnant because their estrogen levels are higher. This results from estrogen's functions in regulating T cell activation and cytokine synthesis, which in turn affect immunological function. As a result, women demonstrate increased susceptibility to rheumatoid arthritis, especially during specific hormonal periods such as pregnancy, and menopause (21). Previous investigations suggest that increased estrogen levels during a female's reproductive years may exacerbate symptoms of RA. The relationship becomes

particularly evident in female whose develop rheumatoid arthritis after birth or throughout the subsequent postpartum period due to rapid hormonal changes (21).

3. Auto-antibodies production and estrogen hormone in RA

The hormone of estrogen may augment the action of particular immune cytokines through routes of signaling that lead to the synthesis of self-antibodies. Estrogen promotes the production of IL-6, which is crucial for stimulating B cells in order to produce antibodies against self-antigens (22). Increased levels of antibodies during elevated estrogen stages, such as gestation, suggest that hormonal fluctuations may influence the onset and progression of disease (22).

4. Estrogen with cytokine in Rheumatoid Arthritis

The developing process of rheumatoid arthritis is influenced by the effect of the hormone estrogen on cytokines associated with inflammation. For instance, women may exhibit reduced disease development as estrogen levels rise, particularly during pregnancy, due to estrogen's anti-inflammatory properties. On rare occasions, increased estrogen levels might lead to the production of pro-inflammatory cytokines, such as TNF-α and IL-1β, which exacerbating symptoms experienced by individuals with rheumatoid arthritis (14). Hormone receptor status, cytokine milieu, and immunological response are some of the factors that affect estrogen's anti-inflammatory and inflammatory mediator activities in rheumatoid arthritis. IL-1β and TNF-α are pro-inflammatory cytokines that contribute to the bone degradation in RA. It has been shown that estrogen can enhance the activity of these inflammatory mediators under some circumstances, which could make the problem worse (14).

Estrogen Receptor alpha (Erα) and Estrogen Receptor beta (ERβ) are expressed on immune cells, including T lymphocyte, B lymphocyte, and macrophages, they have a main effect on the pathophysiology of rheumatoid arthritis (RA). Estrogen decreases the production of pro-inflammatory cytokines such TNF-α and IL-6 and controls immunological responses to provide anti-inflammatory effects (15).

5. Modification of Rheumatoid Arthritis by Estrogen

According to the correlation among estrogen and illness regulation, hormonal changes may impact the severity of RA. Because estrogen can temporarily decrease pro-inflammatory cytokines, it is possible for rheumatoid arthritis to temporarily improve during pregnancy or periods of elevated estrogen levels. When estrogen levels drop after menopause, it can exacerbate joint inflammation and degeneration, making illness more severe (16). Hormonal Phases and Disease Activity: Elevated estrogen levels during pregnancy have been associated with reduced rheumatoid arthritis activity in numerous women. However, post-partum, rheumatoid arthritis symptoms often exacerbate, potentially due to sudden fluctuations in the level of estrogen. This study also assert that postmenopausal women may have heightened joint damage and rheumatoid arthritis severity as a result of the decline in estrogen levels (16).

METHODOLOGY

This review studied the scientific literature that including estrogen in rheumatoid arthritis (RA). Databases such as Google Scholar and PubMed were investigated using keywords such as "estrogen" and "rheumatoid arthritis". This review studied the effects of estrogen and its receptors (ERα and ERβ) on immunity in RA. The study involved an investigation of the role of estrogen in modulating immune responses and interrelating with immune cells.

Epidemiological Studies on the Role of Estrogen in RA

An analysis of prior research on the influence of estrogen in RA patients indicates a complicated interaction among estrogen and mechanism of

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disease. Estrogen, a crucial regulator of immunity, has been thoroughly examined to elucidate its impact on the initiation, advancement, and severity of rheumatoid arthritis, especially in women, due to the gender disparities in RA frequency and progression of the illness.

Table 1: Previous Studies on the Influence of Estrogen in Rheumatoid Arthritis

No.	Mechanism	Finding	Years of publication	References
1	Assess the role of estrogen in modulating immune responses in RA	Estrogen was associated with pro-inflammatory effects and increased disease severity, especially during hormonal changes.	2007	24
2	Investigate estrogen's influence on joint damage progression in RA	Estrogen use, especially after menopause, was linked to more rapid joint damage progression in RA patients.	2008	25
3	Examine the impact of estrogen therapy in postmenopausal women with RA	Estrogen therapy in postmenopausal women helped reduce RA symptoms, particularly in those with early-stage disease.	2009	26
4	Study the effect of estrogen on disease activity in RA	Estrogen levels correlated with RA disease activity, with higher levels seen in women during reproductive years.	2009	27
5	Evaluate the effects of estrogen on RA disease activity in premenopausal women	Higher estrogen levels in premenopausal women were associated with more severe disease activity, particularly during flare-ups.	2015	28
6	Investigate the therapeutic potential of selective estrogen receptor modulators (SERMs) in RA	SERMs reduced joint inflammation and inhibited pro-inflammatory cytokine production in RA patients, suggesting a new therapeutic approach for RA.	2018	29
7	Examine the role of estrogen in modulating inflammation and immune response in RA	Estrogen treatment in RA mouse models reduced joint inflammation by regulating the activity of immune cells, including macrophages and dendritic cells.	2019	30
8	Study the relationship between serum estrogen levels and disease activity in RA	Higher serum estrogen levels were associated with reduced inflammation and joint damage in early-stage RA, while lower levels correlated with increased severity.	2020	31

9	Investigate estrogen receptor gene expression in RA patients	Estrogen receptor (ERα and ERβ) expression was higher in the synovial tissue of RA patients, and their activation influenced the severity of joint inflammation.	2020	32
10	Assess estrogen's role in joint damage and disease severity in early RA	Estrogen levels were inversely correlated with radiological joint damage in early RA, suggesting estrogen might delay disease progression in women.	2020	33
11	Assess the impact of estrogen replacement therapy (ERT) in postmenopausal RA patients	RA symptoms significantly improved in postmenopausal women treated with estrogen replacement therapy (ERT), especially for joint pain and stiffness.	2021	34
12	Investigate the association between estrogen and immune dysregulation in RA	Estrogen influences the balance of Th1/Th2 immune responses in RA patients, with higher estrogen levels skewing the response towards a pro-inflammatory Th1 phenotype.	2021	35
13	Study the effect of estrogen on RA flare-ups in premenopausal women	Estrogen fluctuations during the menstrual cycle were associated with exacerbations of RA symptoms, particularly joint swelling and pain during higher estrogen phases.	2021	36
14	Study the role of estrogen on cytokine production in RA patients	Estrogen treatment in RA patients led to decreased levels of pro-inflammatory cytokines (TNF-α, IL-6), improving disease activity.	2021	37
15	Investigate the association between estrogen and immune dysregulation in RA	Estrogen influences the balance of Th1/Th2 immune responses in RA patients, with higher estrogen levels skewing the response towards a pro-inflammatory Th1 phenotype.	2021	35
16	Examine estrogen receptor signaling in RA synovial tissue	Estrogen receptors (ERα and ERβ) were highly expressed in RA synovial tissues, and their activation led to enhanced pro-inflammatory cytokine release.	2022	38
17	Investigate the role of estrogen in joint damage and progression in RA	Estrogen treatment in postmenopausal women with RA delayed joint destruction and reduced markers of cartilage degradation.	2022	39

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18	Evaluate the impact of estrogen replacement therapy on the progression of RA in postmenopausal women	Estrogen replacement therapy improved RA symptoms, including reduced joint stiffness and pain, in postmenopausal women with moderate to severe disease.	2022	40
19	Investigate the effect of estrogen on the modulation of macrophage function in RA	Estrogen reduced macrophage activation and the production of pro-inflammatory mediators, leading to less severe inflammation in RA patients.	2022	41
20	Investigate the influence of estrogen levels on RA disease activity	Estrogen levels were positively correlated with higher disease activity in premenopausal women with RA, particularly in the presence of autoantibodies.	2023	42
21	Evaluate the effect of estrogen on immune cell function in RA patients	Estrogen was found to modulate T-cell and macrophage activity, increasing the production of pro-inflammatory cytokines in RA patients, leading to exacerbated symptoms.	2023	43
22	Explore the effects of estrogen therapy on RA progression and flare-ups	Estrogen therapy reduced flare-ups and disease progression in RA patients, particularly in those who had low baseline estrogen levels.	2024	44

CONCLUSION

Estrogen's influence on rheumatoid arthritis is multifaceted, impacting the immune system, cytokine production, and disease severity. While it has both pro-inflammatory and anti-inflammatory effects, estrogen appears to contribute to the gender disparity seen in RA, with women experiencing more severe disease during periods of high estrogen levels. Its role in modulating immune responses and joint damage underscores the need for a deeper understanding of estrogen's impact on RA, which could open up new avenues for treatment, particularly in women undergoing hormonal transitions such as pregnancy, menopause, or hormone replacement therapy.

Conflict of Interest

The authors declare that no conflict of interest.

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