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Menopausal Transition and The Development of Rheumatoid Arthritis: An Overview

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic immune-mediated inflammatory illness caused by an accumulation of inflammatory infiltration in the synovial membrane, which leads to the progressive deterioration of joint architecture. Women are three times more likely than men to have RA, with more severe functional loss and disability. The purpose of this review is to study the shifts in the hormonal system brought on by menopause and their potential links with RA. Females are more likely to develop RA as a result of hereditary and environmental interactions of sex hormones and their effects on the immune system. Rapid declines in ovarian function and systemic estrogen have been linked to postmenopausal increases in proinflammatory cytokines such as IL-6, TNF-α, and IL-1β. The majority of the data from the literature review imply that female hormone characteristics that can be influenced by hereditary and environmental variables impact the development of autoimmune illnesses, including RA.

Keywords: Menopause; estrogen; immune-mediated inflammatory illness; sex hormones; IL-6; TNF-α

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic immune-mediated inflammatory disease characterized by synovitis due to the continuous accumulation of inflammatory infiltrate into the synovial membrane, which leads to gradual joint architecture destruction.[1,2] Pain, swelling, joint stiffness, cartilage degradation, and bone degradation are among the symptoms of RA, which can lead to loss of joint function. This systemic disease can also affect organs close to joints, such as blood vessels, kidneys, the heart, lungs, and the liver. Thus, fatigue, malaise, and weight loss are also seen in RA patients.[3] Its prevalence ranges from 0.5% to 2% in the general population.[4] This chronic arthropathy is a burdensome illness that affects not only physical health but also the emotional well-being of the patients.[5] Recent research indicates that pro-inflammatory cytokines produced by T helper type 1 (Th1) cells, such as tumor necrosis factor (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6) play a significant role in the pathogenesis of RA.[6] Expression of RA is influenced by intricate interaction between environmental and genetic variables. A high risk for RA, an earlier beginning of the disease, and more severe bone erosions are connected to the common epitope. Smoking is a crucial and manageable potential risk for the onset of RA.[7] Environmental factors are thought to be responsible for about 70% of all autoimmune diseases and 80% of all chronic illnesses. There is a lot of evidence to support the intricate interactions between diverse environmental and genomic components for illness etiology, and these high numbers show that environmental exposures are a significant contribution to disease. During the clinical and preclinical stages of a disease, manipulating environmental triggers and the host immune system will provide considerable knowledge and effective timely detection for several conditions.[8]

Based on the presence of autoantibody rheumatoid factor (RF), RA can be classified into two types: seropositive rheumatoid arthritis and seronegative rheumatoid arthritis.[9] Seropositivity was found in 60-80% of those diagnosed with RA who had the antibody Rheumatoid Factor (RF). These can be detected from blood tests even five to ten years before clinical symptoms of RA, called the "pre-RA phase." RF can be detected in the blood tests of patients with other infectious conditions. Therefore, the presence of RF with anti-cyclic citrullinated peptides (anti-CCPs) or anti-citrullinated proteins (ACPA) confirms seropositive RA. The seronegative type of RA is relatively less severe. RF is absent from the serum of seronegative RA patients. Clinical symptoms, laboratory tests for anti-CCPs or ACPA, and X-rays are used to diagnose and confirm seronegative RA.[10]

First-degree relatives of RA patients are more susceptible to the disease, indicating a hereditary genetic influence in RA pathogenesis.[11,12] Many studies conducted to detect the interaction of environmental factors in RA

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development have conflicting results.[13,14] Women are three times more likely than men to have RA, with more severe functional loss and disability.[15] In women, the fifth decade is the peak age of RA incidence, which is also the time of hormonal changes.[14] Conditions such as pregnancy, contraception, and menopause, which are associated with reproductive and endocrine changes, may influence the progression of RA.[16] Menopause, which typically occurs between the ages of 45 and 52 in most women, is marked by hormonal changes and the cessation of the menstrual cycle. There will be 47 million additional women born each year by 2030, bringing the total number of menopausal or postmenopausal women in the world to 1.2 billion.[17] Several observational and epidemiological studies imply that sex hormones have a role in the genesis and progression of RA.[18,19] There is evidence of a strong association between RA and sex hormones in women.[16]

The goal of this review is to examine the shifts in the hormonal system brought on by menopause and any potential links to RA. To better understand these aspects, we'll give an overview of menopause and RA, then talk about how the two might be related. We'll also cover emerging trends about the function of menopause and hormonal factors in rheumatoid arthritis. We have reviewed the available national and international literature including research articles and other published review articles which dealt with the studies which point out the relationship between female menopausal hormone and the onset of rheumatoid arthritis. ScienceDirect, PubMed, Google Scholar etc were used for the extensive literature search.

2. MENOPAUSE

Menopause is defined by the World Health Organization (WHO) as the cessation of menstruation for more than 12 months.[20] As women enter their forties, they will experience hormonal changes known as menopausal transition, which will last several years. Ovarian function declines due to the depletion of ovarian follicles, leading to the appearance of menopausal symptoms.[21,22,23] Follicle-stimulating hormone (FSH), oestradiol (E2), inhibin B, and anti-Mullerian hormone are the major hormones in the hypothalamic-pituitary-ovarian axis and are indicative of ovarian aging.[24] Inhibin B and E2 modulate FSH release by the anterior pituitary through a negative feedback mechanism. As women age, the follicle pool shrinks, resulting in a drop in inhibin B levels. A lack of inhibin-mediated FSH secretion restraint causes an increase in circulating FSH levels. During the menopausal transition, E2 levels fluctuate with FSH levels.[25,26,27] A rise in FSH levels causes the recruitment of more follicles in a particular cycle, resulting in a higher serum E2 level that may be adequate for endometrial stimulation. Over time, this will eventually lead to menopause.

During menopause, plasma E2 levels decrease dramatically. When the postmenopausal ovary ceases to release estrogen into circulation, peripheral conversion of androstenedione into oestrone will become prominent. 5% of this oestrone will be converted to E2 by 17-hydroxysteroid dehydrogenase.[24,29] This reversible reaction depends on the oxidoreductase state of the cell. During the first year of menopausal anovulation, there will be a decline in oestrone production to a certain level, and then it stabilizes.[30] Menopausal anovulation will also lead to the decline of progesterone production, but the postmenopausal ovary will continue to release testosterone into systemic circulation.[21,22,24]

3. RA PATHOPHYSIOLOGY

Although the etiology and pathogenesis of RA are unknown, it is thought that genetic and environmental variables, as well as autoimmunity, play major roles in RA susceptibility.[31] The immunological process that leads to RA can begin many years before the appearance of symptoms. This can be mentioned as the pre-RA phase.[32] Genomic structural modification by epigenetic and environmental factors triggers the production of self-antigens (immunoglobin, vimentin, type 2 collagen, etc.) in susceptible individuals. Peptidyl arginine deaminases cause citrullination of the arginine residues of these proteins, which leads to the formation of citrulline.[33,34] Fibrin, fibronectin, type 2 collagen, vimentin, histones, enolase, Epstein-Barr nuclear antigen, and other citrullinated proteins are examples.[35] Due to the susceptibility of their HLA-DR1 and HLA-DR4 genes, RA-susceptible individuals' immune systems will be unable to recognize citrullinated proteins as self-structures.[36]

Those citrullinated proteins identified as antigens are then carried by antigen-presenting cells (APC), forming a complex that can initiate an immune response. The APC-antigen complex activates CD4 helper T cells after reaching the lymph node. B cells in the germinal center of the lymphocyte also get activated along with T cells by the co-stimulation process.[37,38] The activated B cells then undergo proliferation and differentiation into plasma cells. Proliferation and differentiation of activated B cells by somatic hypermutation and class switch recombination produce autoantibodies.[39] Autoantibodies are unable to distinguish between self and non-self-structures, resulting in the unintentional attack of self-tissues and organs.[40]

Rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) are two such autoantibodies.[41] IgM antibody-derived RF targets IgG antibodies' constant Fc domain. The complex formed by RF with complementary proteins and IgG can migrate to the synovial fluid. ACPA is more specific for RA and forms complexes with citrullinated proteins that get accumulated in synovial fluid, leading to the over-activation of the complementary system. through an enzymatic cascade of complementary systems.[18] Further joint injury and inflammation occur as a result of the enzymatic cascade of a complementary system containing the family of nine proteins. T cells produce cytokines such as interleukin-17 and interferon-γ after entering the joints from the circulation. It also causes macrophages to produce inflammatory cytokines

like interleukin-1β (IL-1β) and interleukin-6 (IL-6) as well as tumor necrosis factor- (TNF-α). All these mediators lead to the proliferation of synovial cells. Synovial macrophages also cause stimulation of both fibroblast-like synoviocytes (FLS) and osteoclast activity, further leading to bone erosion. FLS causes the secretion of protease enzymes by cartilage through Matrix Metalloproteinase (MMP) production, which leads to the destruction of protective articular cartilage. RANKL is also stimulated by FLS, which aids the attachment of T helper cells to the RANK protein of the osteoclast, which eventually leads to bone erosion.

Excessive proliferation of immune cells and synovial cells causes inflammation of the synovial membrane with granulation. This formation is called a pannus, which can cause progressive degradation of cartilage and soft tissues and also results in weakened bones at the area of invasion (Fig. 1). Simultaneously, these chronic inflammatory conditions will lead to angiogenesis at the joints, which leads to the infiltration of inflammatory chemicals into the site. This will further worsen the condition by causing inflammation and the progressive destruction of other joints of the body in the same way that it causes deformity (Fig. 2). Arthritic joints initially appear reddish, swollen, and painfully palpitating. As the disease progresses, it becomes stiff after a certain period of inactivity, especially in the morning time.[40,41]

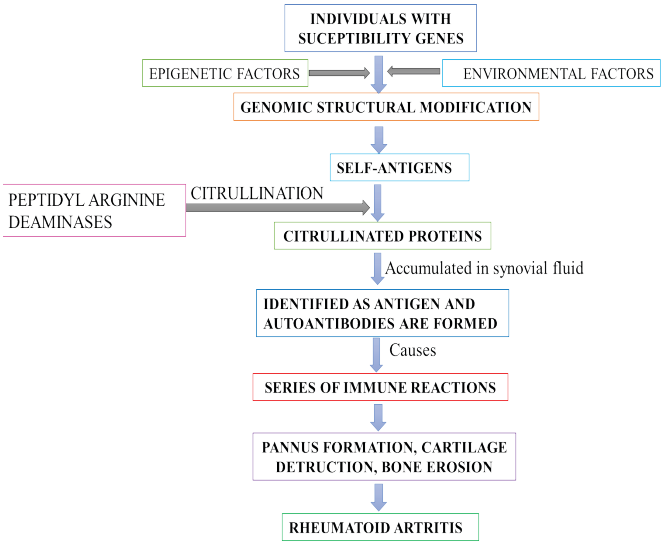

Figure 1. Individuals with susceptibility genes are prone to genomic structural modification by epigenetic or environmental factors. This leads to the formation of self-antigens, which get citrullinated by the peptidyl arginine deaminases. These citrullinated proteins get accumulated in the synovial fluid and are identified as antigens by the immune system, leading to the formation of autoantibodies. This causes a series of immune reactions that cause pannus formation, cartilage destruction, and bone erosion, indicating RA.

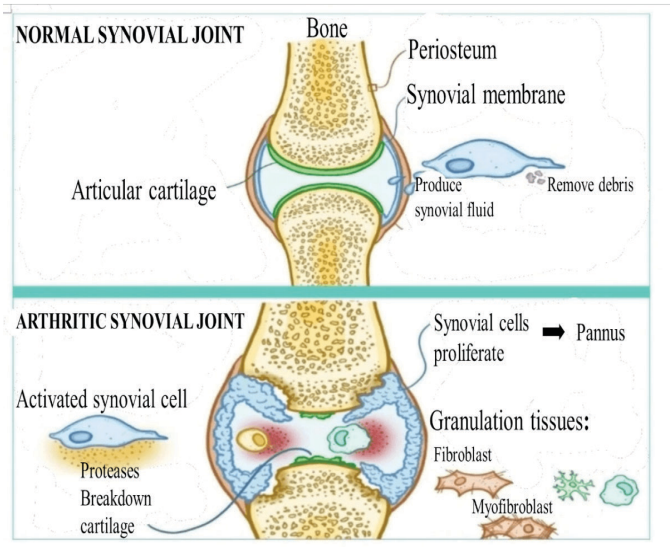

Figure 2. Normal and arthritic synovial joints (modified image of UR Sharma et al., [40]

4. RECENT DEVELOPMENTS IN THE STUDY OF MENOPAUSAL HORMONE ASSOCIATION IN RA ONSET AND PROGRESSION

Mollard*et al*., (2018) studied the influence of menopause on the functional state of RA-affected women using data from the National Data Bank for rheumatic disease. They observed that there is a worse functional decline in RA-affected postmenopausal women when compared to premenopausal women with RA. This suggests an association between the menopausal transition of bodily functions and the worsened progression of RA, suggesting a role for menopausal hormones in RA.[15]Alpizer Rodrigues *et al*., (2018), through SCQM cohort research, examined the involvement of reproductive and menopausal variables in the functional and structural development of RA. They aimed to investigate if there was a link between female reproductive and menopausal variables and the advancement of functional and structural joint deterioration in women with RA. In a study conducted with a total of 1667 women, 1025 women (61%) had a higher functional disability and erosion scores than premenopausal women with RA. Their findings showed that RA-affected women who reach menopause at a young age are more likely to develop comorbidities and have less favorable functional outcomes.[42]

Engdahl*et al*., (2018) reported a potential explanation for the increased prevalence of RA in postmenopausal women by studying the estrogen-based molecular mechanism. They suggested that estrogen (E2) regulated IgG-Fc sialylation by inducing S6gal-1 expression. Thereby, it will form a protective, anti-inflammatory environment. In postmenopausal women, there will be a menopausal decrease in estrogen, making them more vulnerable to disease and resulting in low sialylation and a pro-inflammatory pattern.[43] Tariq Ali *et al*., 2019 investigated menopausal changes in 17β-estradiol hormone and Interleukin-1 in women with RA. This study strongly suggests that a

decrease in 17β-estradiol hormone, by raising the levels of proinflammatory IL-cytokines, menopause significantly contributes to the onset of RA.[44] By a countrywide cohort study involving 1.36 million women, Eun*et al.,* (2020) looked into the relationship between menopausal variables and the probability of postmenopausal women developing seropositive RA. Further, this study supports the Nurses' Health Study by confirming a minor association of seropositive RA with menopausal age. They concluded that reproductive factors do not have any significant role, but hormone replacement therapy has a significant role in developing seropositive RA. Through a Mendelian randomization study.[45] Zhu *et al*., 2021 attempted to establish a causal relationship between hormonal transition in women and RA, which is more prevalent in females. Even though they strongly believed in the association, due to the limitations of the study, they were unable to establish a causal link. They suggested that future preventive interventions should focus on understanding the precise role of potentially modifiable hormonal factors.[46] Salliot*et al*., 2021, assessed the relationship between RA incidence and female sex hormones influences through a prospective cohort involving French women. They discovered that early pregnancy and early menopause in smokers increase the risk of RA. They suggested that an acute decline in ovarian function might contribute to the development of RA by activating autoimmunity.[47]

Park EH *et al*., found that early menopause was significantly associated with enhanced clinical outcomes, a decline in functional ability, and a reduction in quality of life related to one's health. Their findings provide credence to the idea that postmenopausal women with RA have lower exposure to reproductive hormones in their life time, which influences the course of the disease and the development of concomitant conditions. They recommended that when assessing and treating female RA patients, menopausal status and the time of menopause be thoroughly investigated. Also, they stated RA affected individuals who experience menopause at an early age noted significant variations in symptom severity and patient reported findings.[48]

5. DISCUSSION

The changes in the hormonal environment that occur as a result of menopause and their possible association with rheumatoid arthritis are discussed here. Female hormonal changes after menopause, as well as menopause at a young age, can both contribute to the development of RA. In these conditions, an abrupt reduction in ovarian function and/or estrogen bioavailability is observed. Throughout the lifetime of a woman, there will be fluctuations in the serum levels of estrogen and progesterone. During pre-menopause and post-menopause, the timing of exposure to these hormones has a role in the development of RA. The higher prevalence of RA in females can be explained in terms of the genetic and environmental interactions of sex hormones and their interaction with the immune system.

A rapid decline in ovary function and systemic estrogen during menopause is associated with a spontaneous increase in pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β. Estrogen has stimulatory and inhibitory effects on the immune system. During the preovulatory period, estrogen promotes the survival of autoreactive T and B clones by stimulating B cells and the Th2 response. Cell-mediated responses, such as Th17 cell differentiation, are also inhibited. Estrogen binds to estrogen receptors and gets distributed in various tissues at different levels. ER- expression is higher in RA synovial tissue than ER-. ER- expression increases during inflammation or hypoxia, stimulating peripheral blood mononuclear cells (PBMC) to produce TNF-α and IL-6. Progesterone stimulates Th2 responses and inhibits Th1 and Th17 cells. The rapid decrease in progesterone causes an increase in IL-1β and TNF-α expression. In RA patients, there will also be an increase in the conversion of androgen to estrogen due to the stimulatory effect of pro-inflammatory cytokines on the aromatase enzyme.

Around menopause, there will be a depression in the progesterone and estrogen levels in the female body. (Fig.3) But there will be a slight elevation in the androgen level, which will be later converted to estrogen by the aromatase enzyme. Progesterone deficiency stimulates PBMC to produce cytokines such as TNF-α, IL-6, and IL-1β. During hypoxia or inflammation, there will be more ER-β than ER-α expression, which will eventually

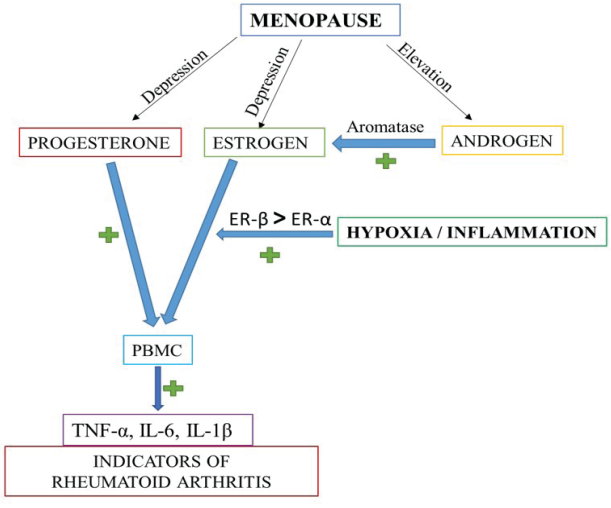

Figure 3. There will be a drop in progesterone and estrogen levels in the female body around menopause. However, there will be a minor increase in androgen levels, which will be converted to estrogen by the aromatase enzyme later. A decrease in progesterone levels in the PBMC induces the production of cytokines such as TNF-α, IL-6, and IL-1β. During hypoxia or inflammation, ER-β will be expressed more than ER-α, which will eventually stimulate PBMC to produce cytokines. Since these cytokines are linked to rheumatoid arthritis, the link between menopause and rheumatoid arthritis can be explained.[49,50]

stimulate PBMC to produce cytokines. The correlation between menopause and rheumatoid arthritis can be explained by the strong relationship between these cytokines and the onset of RA. (Fig. 3).

6. CONCLUSION

The systemic autoimmune disease RA is predominant in women, and its severity increases after menopause, suggesting a role for female hormones in the underlying mechanism of RA. Most of our findings suggest that female hormonal features, which are modifiable by genetic and environmental factors, influence in the development of autoimmune diseases such as RA. The immune system is both stimulated and inhibited by estrogen. Therapies targeting the maintenance of estrogen at a particular level will be useful in managing the severity of RA in women, especially in the post-menopausal phase. However, a strong association between these factors should be established with more evidence to develop novel treatment strategies targeting female hormones such as estrogen to manage the severity of RA in women.

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