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SEX HORMONES AND RHEUMATOID ARTHRITIS: A REVIEW OF THEIR ROLE IN DISEASE DEVELOPMENT: REVIEW ARTICLE

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ABSTRACT

Rheumatoid arthritis (RA) is a kind of persistent inflammation of the joints that affects 0.5 to 1.0% of people worldwide. It can cause increasing disability, which results in a considerable socioeconomic burden. RA can be caused by genetic and environmental factors. Both genetic and environmental factors can increase the likelihood of developing RA. Hormonal factors have also been identified as risk factors for RA. Sex hormones have an impact on both males and females throughout their entire brain via receptors, both genomic and nongenomic. Sex hormones have the power to modify behavior, change the way that neuronal systems are organized and operate, and even offer neuroprotection. Progesterone, androgens, and estrogens all influence the immunological response. While progesterone and androgens are naturally occurring immune suppressors, estrogens can strengthen humoral immunity. Research point to a possible involvement of sex hormones in the pathogenesis of RA. The highest incidence of RA at menopause, decreased disease activity during pregnancy, and postpartum flare are indicative of this. The findings that demonstrate a link between sex hormones and the pathogenesis of rheumatoid arthritis are the main topic of this review.

KEYWORDS: Autoimmune Diseases, Rheumatoid Arthritis, Sex Hormones, Estrogen, Androgens, Testosterone.

INTRODUCTION

Rheumatoid Arthritis (RA) is a condition of chronic joint inflammation that affects around 0.5-1.0% of the population. This disorder can lead to increasing levels of disability, which in turn results in a significant socioeconomic burden [1]. The pathophysiology of RA involves the persistent inflammation of the synovial membrane, which causes damage to the articular bone and cartilage [2-4].

Synovial inflammation brought on by immunological activation causes joint swelling in rheumatoid arthritis. Infiltration of leukocytes into the normally sparse synovial compartment is the disease's defining feature [5]. Studies showed that women are three times more likely than men to develop RA, particularly during childbearing years (25-55 years old). This suggests estrogens might be protective in pre-menopausal women but detrimental after menopause [6]. RA symptoms often improve or even go into remission during pregnancy, further indicating hormonal influences. This improvement is likely due to the immunosuppressive effects of pregnancy hormones like progesterone and placental hormones [7]. Futhermore, RA activity often increases after menopause, possibly due to the decline in estrogens and their anti-inflammatory properties [8]. This review was aimed to critically analyze the current understanding of the relationship between sex hormones and RA.

Impact of sex hormones in autoimmune diseases

The term "autoimmune diseases" refers to a class of more than 70 distinct clinical disorders that arise when the body's immune system unintentionally targets healthy cells. These diseases can impact almost any part of the body, including the joints, skin, and internal organs. Interestingly, there is a notable distinction in the occurrence of autoimmune diseases amongst men and women. The reasons for these gender-based differences are not yet fully understood and are currently the subject of ongoing research [9].

Autoimmune diseases arise due to the malfunctioning of the acquired immune system. B and T cells make up the acquired immune system, which are responsible for identifying and attacking foreign pathogens in the body. However, in autoimmune diseases, these cells wrongly recognize and attack the body's cells and tissues as foreign, causing inflammation and damage to various organs and tissues in the body [10].

Interestingly, the acquired immune system works differently in males and females. The main hormone involved in female sex, estrogen, stimulates immunological responses that are controlled by B cells and CD4+ TH2 cells. These cells are responsible for producing antibodies and starting the immune system to protect the body against parasites and allergies. On the other hand, the main hormones associated with male sex, androgens, stimulate CD4+ TH1 and CD8+ cell activity. These cells are responsible for producing a cell-mediated immune response that fights off viruses and other intracellular pathogens. This difference in immune system function may explain why autoimmune diseases tend to be more prevalent in women than in men. It also suggests that different treatment approaches may be more effective for men versus women based on their hormonal profiles and immune system function [11].

It is worth noting that there exists a complex relationship between sex hormones and the immune system's functionality. Recent Research has indicated that estrogens, the primary female sex hormone, have a positive impact on humoral immunity, which is the aspect of the immune response that produces antibodies to fight off infections. On the other hand, androgens and progesterone, the primary male and female sex hormones respectively, are known to naturally suppress the immune system. Furthermore,

it is important to mention that chronic pain conditions exhibit significant differences between genders in terms of how often they occur, their intensity, and how much they affect daily functioning. These differences are believed to be associated with hormonal fluctuations, particularly in women. For example, women tend to experience more chronic pain conditions than men and are more likely to report greater pain intensity and disability as a result [12].

The effects of sex hormones, specifically prolactin, estrogen, progesterone, androgens, on the immune system have been extensively studied. There has been a lot of research in how these hormones may affect a person's vulnerability to autoimmune disorders (ADs). The innate and adaptive immune systems, which are vital parts of the body's defense against infections, are impacted by these hormones, according to studies. The innate immune system provides immediate, nonspecific responses to infections, while the adaptive immune system provides a more specific response to pathogens and has the ability to remember past infections for faster responses in the future. The impact of sex hormones on these systems has been found to vary depending on the type of hormone and the stage of the menstrual cycle. For example, estrogen has been shown to enhance both innate and adaptive immune responses, while progesterone has been found to suppress immune responses. In general, more research in this field is necessary to better understand the mechanisms behind autoimmunity and create effective therapies, as the intricate interactions between sex hormones and the immune system highlight [13].

Sex hormones in rheumatoid arthritis disease

Rheumatoid arthritis pathogenesis

This reveiw does not have the space to explain the pathophysiology of rheumatoid arthritis in detail; instead, the reader is directed to other recent, very good evaluations [14, 15]. In conclusion, it is now understood that RA results from the complex interaction of genes and environment, and that inflammation in synovial joints is the resultant loss of immunological tolerance. The greatest genetic component is the human leukocyte antigen (HLA) class II molecule HLA-DRB1, which is present in over 80% of cases and contains the common epitope of the HLA-DRB1-04 cluster [16]. It is also related to how severe the condition is [17]. Years before symptoms manifest, the etiology of RA is thought to start, and it most likely involves environmental factors, smoking being the most well-established producing post-translational alterations [18].

Antigen-presenting cells use these pathways to initiate an adaptive immune response that results in the generation of the signature autoantibodies ACPA and RF (which target immunoglobulin G) [15].

Interactions between pro-inflammatory cytokines, primarily interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-α), and immune cells, such as T and B cells, plasma cells, and monocytes, result in an infux and local activation of inflammatory cells in the synovium. Synoviocytes that resemble macrophages proliferate and emit pro-inflammatory mediators such IL-6, IL-1, and TNF-α. Mature B cells that generate RF and ACPAs as well as CD4+ T cells are among the immune cells that have penetrated. The synovial membrane swells and new blood vessels grow. The many osteoclasts in the synovium are the primary source of bone erosion, whereas the matrix metalloproteinases released into the synovial fluid by synoviocytes that resemble fibroblasts are responsible for cartilage degradation.

The role of sex hormones in development of RA

There is evidence to suggest that the development of RA may be influenced by sex hormones. In fact, RA has been found to have its highest incidence during menopause, which suggests a strong correlation between hormonal changes and the onset of the disease [19]. Additionally, it has been observed that disease activity tends to decrease during pregnancy, while there is an increased frequency of flares in the post-partum period [20].

There are several theories as to how sex hormones may be involved in the development of RA. One theory is based on the higher incidence of the disease in males, which suggests that male sex hormones may be protective against the disease. Another theory is based on the higher frequency of flare-ups in women after giving birth, which suggests that female sex hormones may contribute to the development of RA. It is also believed that sex hormones might have a regulatory effect on the immune system, which could explain their potential role in the development of RA. Overall, the relationship between sex hormones and RA is complex and multifaceted, and further study is needed to fully understand the fundamental processes involved [21]. The development of RA may be associated with low testosterone levels, as the disease is less prevalent among men, and the risk of RA increases as they age, and their androgen levels decline. Testosterone is a straightforward and stable hormone to measure compared to estrogen, which tends to fluctuate [21]. Pro-inflammatory cytokines have been found to stimulate the hypothalamic-pituitary-adrenal axis, but at the same time inhibit the hypothalamic-pituitary-gonadal axis, leading to the possibility that low testosterone levels may result from the inflammatory disease. Alternatively, the reduced levels of testosterone that have been measured could indicate the role of androgens in the pathogenesis of RA [22]. Sex-specific factors affecting rheumatoid arthritis are compiled in Table (1).

Table:1 *(Sex-specific factors affecting RA.)*

1. Hormones	Estrogen's impact on the immune system "induction of Tregs, supportive and anti-inflammatory effects" [23]. The effects of Progesterone on immunity (Treg induction and anti-inflammatory effects) are significant [23]. Effects of androgens on immune function (anti-inflammatory effects) [24]. High aromatase activity affects the estrogen/androgen balance of the synovial fluid [25].
2. Genetic factors	Single nucleotide polymorphisms of the CYB5A gene in RA females [26]. TIMP1 and IL-9R, both X-encoding genes, exhibit single nucleotide polymorphisms [27].

3. Clinical phenotype	Compared to women, men's illness courses are less severe, and they react better to therapy [28]. Amelioration of RA in pregnant females [29].

Sex hormones signaling in rheumatoid arthritis

A coordinated immune response is necessary for effective immunity, and this response is influenced by genetic, environmental, and hormonal variables. These factors can alter an individual's immune system's response to an infection or damage in a way that is specific to their sex [30]. Progesterone, testosterone, and estrogens are the three main steroid hormones with which the immunological response has been examined. These hormones affect the expression of genes by binding to certain cell membranes and nuclear-associated receptors on or in immune cells. The beta (ERβ), alpha (ERα), and androgen receptor (AR) are the receptors that cytoplasmic heat shock proteins bind to. In response to ligand stimulation, they either form direct bonds with certain gene promoter areas, such as the interferon (IFN)γ gene, or they form indirect bonds with transcription factors, such as NFκB, to initiate gene transcription [31]. Sexual hormones also modify immune cell activity through the development of hormone receptors on non-nuclear membranes. Nuclear receptors take longer to signal than membrane hormone receptors. By starting up MAPK, ERK, and other kinase signal pathways, it can start gene transcription. Alternatively, calcium influx and glutamate receptor activation can start non-transcriptional signals [32].

The immune reaction changes according to the kind of cell, the antigen that produces the inflammation, the tissue where the inflammation occurs, the dose of the antigen, the age of the cell or animal, and the genetic background of the individual. In other words, the immune response is fully context dependent. It is important to remember that biological sex plays a major role in determining the kind of immune response the body will mount against any given antigen. Sex hormone receptors are found on the surface of immune cells, where they can interact as a part of the immunological synapse during antigen presentation, while being expressed intracellularly the majority of the time [31].

Estrogen

Estrogens and the immune system have complex interactions that can be pro- or anti-inflammatory, depending on the cell type and quantities involved [33]. The estrogen-ERα complex, which is important for B cell activity, binds physiologically to the AICDA gene promoter and increases the synthesis of activation-induced cytidine deaminase (AID). This enzyme is the primary modulator of somatic hypermutation and class switch recombination. Thus, estrogens encourage B cells to switch their immunoglobulin class, which is why it makes logical that they would be detrimental to autoimmune diseases characterised by the production of autoantibodies [34].

Hematopoetic precusors in the bone marrow go through an early developmental stage before moving to the thymus during T cell ontogeny. Both positive and negative selection are at play in this situation. Except for a small percentage of CD4+ cells that live and develop into regulatory T cells, or Treg, T cells that aggressively react to the major histocompatibility complex antigen are destroyed. Through its regulation of the negative selection process, the transcription factor AIRE encourages self-tolerance.

This protein has been linked to autoimmunity's sexual dimorphism; after puberty, women express less AIRE than do men [35].

AIRE expression is reduced in male castrated mice, however there is no difference in expression between the sexes in ERα defective animals. Furthermore, it was discovered that methylation of CpG sites in the AIRE promoter reduces AIRE production in human thymic tissue when estrogen is administered [35].

However, it has been found that oestrogens directly lower T cell inflammation in a variety of ways. It has been shown that in vitro production of pro-inflammatory interleukin (IL)-17 and TNFα in T cells from both healthy donors and patients with active RA is reduced by the natural agonist of ERβ, silibinin [36].

The epigenetic modifier microRNA-155's expression was downregulated to facilitate this impact. Furthermore, it has been shown that silibinin kills human RA synoviocytes in vitro and reduces the production of inflammatory cytokines in rats with collagen-induced arthritis [37].

The postpartum flare in CIA was reduced by exogenous estrogen treatment [38]. On the other hand, high-potency estrogen alone [39] or pregnancy-like dosages of progesterone or estradiol [40] reduced joint inflammation in arthritis-prone mice that were not pregnant. Treating non-pregnant SKG mice (a model of human RA) with either progesterone at pregnancy-like levels has been shown to reduce joint inflammation in a pregnancy-induced manner [40].

Progesterone

Unlike estrogens, which have contradictory effects on inflammation, progesterone has broad anti-inflammatory properties. These include inhibiting the TH 1 and TH 17 response, suppressing AID (resisting the effects of estrogens), and suppressing NK cells, neutrophils, and macrophages [41]. Human T cells that are exposed to progesterone produce more IL-4 and IL-10, which in turn triggers the TH2 response [42]. During pregnancy, lymphocytes produce progesterone-induced blocking factor, a protein with strong anti-natural killer (NK) cell activity, in conjunction with progesterone receptor expression [43].

It has been shown that progesterone suppresses mTOR signaling to generate FOXP3+ Tregs from naïve murine CD4+ T cells [44]. Progesterone also promotes and inhibits the differentiation of human fetal cord blood T cells into Tregs and TH17 cells [45]. Tregs in MS have significant expression of estrogen and progesterone receptors, and each hormone enhances the suppressive potential of Tregs in vitro [46]. It has been shown that progesterone, at doses similar to those seen in the placenta, reduces ex vivo CD4+ T cell activation from healthy human females in a dose-dependent way, as evidenced by CD69 and CD25 expression. Significant transcriptome changes were also found by RNA sequencing analysis, including the downregulation of immune-related genes and pathways, such as STAT3 and STAT1, which are essential for RA [47].

Androgens

In vivo, androgens have several anti-inflammatory properties, such as reducing the quantity of pro-inflammatory cytokines released by monocytes, including TNF, IL-1, and IL-6, and inhibiting the production of antibodies and B cell lymphopoiesis [48].

Blood testosterone levels are often lowered in inflammatory rheumatic illnesses because inflammatory cytokines such as TNF, IL-1, and IL-6 activate the aromatase enzyme in immune cells and fibroblasts. It is also known that androgens bind to and upregulate tyrosine-protein phosphatase non-receptor type 1 (PTPN1), which plays a number of functions in immunological response and cell proliferation. Tyrosine kinase 2 and janus kinase (JAK)-2 are two elements of the JAK-STAT pathway that are inhibited by PTPN1 and are necessary for TH1 cell-mediated immunological responses as well as the production of IL-12 and IFNγ [49].

Unlike oestrogens, androgens activate AIRE transcription by drawing androgen receptors to AIRE promoter regions; this leads to increased expression in the thymus of humans and male vs female mice [50]. Male sex and testosterone treatment protected against multiple sclerosis in a mouse model; however, this effect has not yet been investigated in models of rheumatic disorders, such as RA [50]. Table (2) lists current research on the correlation between sex hormones and RA.

Table: 2 *(Recent studies investigating the role of sex hormones in RA.)*

Number	Aims	Findings	Reference
1.	This study investigated the association between serum testosterone levels and the risk of developing arthritis.	This large-scale study found a significant negative association between testosterone levels and arthritis. Individuals with lower testosterone were more likely to have arthritis, particularly women and those with a higher body mass index (BMI).	[51]
2.	To review the current understanding of how sex hormones, particularly estrogen, progesterone, and androgens, influence the development and progression of rheumatoid arthritis (RA).	The study suggests a complex relationship between sex hormones and RA. Estrogen levels may play a protective role before menopause but contribute to increased disease activity after menopause	[52]

3.	To explore the potential benefits of estrogen in RA treatment based on its anti-inflammatory properties and effects on the immune system.	The study discusses how estrogen might suppress inflammatory responses and antibody production in RA. It highlights the need for further research to determine the therapeutic use of estrogen in RA management.	[53]
4.	To investigate the multifaceted role of estrogen in RA, considering its influence across various female hormonal stages like menarche, menstruation, pregnancy, and menopause.	The study reveals that estrogen levels can both increase and decrease the risk of RA development depending on the hormonal stage. It emphasizes the need for tailored approaches to understand how estrogen affects RA in different women.	[54]
5.	Examine the relationship between the age at which a woman goes through menopause and the course of her rheumatoid arthritis in postmenopausal women.	When compared to women whose menopause occurs at the normal timing, early menopause (before the age of 45) was linked to poorer disease activity.	[55]
6.	Investigate the relationship between the usage of sex hormones and remission rates in rheumatoid arthritis patients undergoing particular therapies.	The use of exogenous sex hormones has been associated with a much-increased likelihood of obtaining illness remission, especially in perimenopausal women.	[56]
7.	The purpose of this study was to investigate the relationship between hormonal and	There is a link between certain hormonal and reproductive variables and an increased risk of RA. For female RA patients, hormonal	[57]

	reproductive variables and the risk of rheumatoid arthritis (RA) in women from the large UK Biobank cohort.	and reproductive aspects should be considered while assessing risk and creating treatment strategies.	
8.	It is currently unclear how these hormones relate to the activity of the illness, and research in this region of the world has not focused much on whether hormone imbalance increases the severity of RA. The goal of the study was to clarify this fact.	By using linear logistic regression analysis, it was discovered that there was an inverse association between disease activity (as determined by DAS28) and serum DHEAS and testosterone, and a statistically significant link between disease activity and serum progesterone, FSH, and prolactin. Target clinical goals in RA were shown to be related with low serum levels of prolactin and FSH and high levels of testosterone and DHEAS (i.e., remission and low disease activity).	[58]

CONCLUSIONS AND FUTURE PERSPECTIVES

The relationship between RA and sex hormones is multifaceted and complex. While evidence suggests an impact of sex hormones in activity and severity of disease, the exact mechanisms and optimal hormonal interventions remain unclear. To understand these complex interactions, further studies is needed to develop targeted therapies based on individual hormonal profiles. Further researches are needed to answer gaps in knowledge and areas for further research. There are some potential research directions, such as: 1. Investigating the role of specific hormone receptors and signaling pathways in RA. 2. Developing personalized hormonal interventions based on individual hormone profiles and RA phenotypes. 3. Exploring the combined effects of hormonal and conventional RA therapies.

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