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REVIEW

Unraveling the hormonal approaches for the treatment of rheumatoid arthritis and its complementary interventions

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Abstract

Rheumatoid Arthritis (RA) is an autoimmune, chronic, systemic inflammatory disease that causes redness, swelling, stiffness, and joint pain. It is a long-lasting disease that can have a widespread impact on the body, often affecting the hands, feet, and wrists. The immune cells, such as dendritic cells, T cells, B cells, macrophages, and neutrophils, play a significant role in bone degradation and inflammation. Several cytokines, including TNF-α and IL-17A, play a significant role in causing bone erosion, cartilage deterioration, and joint inflammation. Progesterone and estrogen have a crucial impact on the pathophysiology of RA, influencing the immune system. Research has demonstrated that hormone replacement therapy (HRT) can effectively reduce inflammation, improve disease activity, enhance joint health, alleviate pain, and promote bone strength. Treatments such as tamoxifen and raloxifene, known as selective estrogen receptor modulators (SERMs), are effective against chronic inflammatory illnesses like RA. The treatment with Gonadotropin-releasing hormone (GnRH) has an impact on the hypothalamic–pituitary–gonadal axis, which in turn affects the activity of RA illness. These alternative treatments hold promise in enhancing well-being and alleviating joint pain for individuals with RA.

Keywords Estrogen · Hormones · Inflammation · Progesterone · Rheumatoid arthritis · Testosterone

Introduction

"Rheumatoid arthritis" emerged in the nineteenth century and earlier it was known as "primary asthenic gout" before being renamed as "rheumatoid gout" (Gilbert and Lamacchia 2023). Rheumatoid Arthritis (RA) is an autoimmune, chronic, systemic inflammatory disease that causes redness, swelling, stiffness, and joint pain (Sugiyama et al. 2024; Black et al. 2023). It also primarily impacts the synovial tissues with symmetric involvement of peripheral joints, hands, feet, wrists as well as affects the organs, peri-articular soft tissues leading to the deterioration of articular cartilage, furthermore affecting the non-articular muscular structures (tendons, ligaments, fascia), and marginal bone which ultimately results in irreversible joint destruction (Cojocaru et al. 2010; van Delft and Huizinga 2020; Dong et al. 2018; Díaz-González and Hernández-Hernández 2023). The increase in local inflammation is due to citrullinated proteins (CP) which are present in synovial fluid (SF) in RA joints (Conforti et al. 2021) and increase fatigue with impairment of participation in recreational, societal, and occupational roles (Black et al. 2023). The proliferation of synovial cells in joints occurs due to the overproduction of

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pro-inflammatory cytokines, such as tumor necrosis factor (TNF) and interleukin-6 (IL-6) (Conforti et al. 2021). RA patients commonly exhibit autoantibodies, such as rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA); where ACPA plays a crucial role in the extent of joint damage (van Delft and Huizinga 2020; Conforti et al. 2021). RA is diagnosed by the RF, which are abnormal antibodies (IgG) present in blood that react with antigens forming an antigen–antibody complex that leads to pain and inflammation of the synovial membrane (Kaur A et al. 2012). Smokers (ACPA production increases), women, and those with a family history of the illness are particularly prone to being affected by RA. (Gilbert and Lamacchia 2023; Conforti et al. 2021; Oliver and Silman 2006). All age groups of women, men, and children can be affected by RA, whereas women suffer two or three times more with increasing age and commonly occurring at the age of 60–70 in females (Black et al. 2023). An early onset of menopause has repeatedly been linked to a higher risk of developing RA. Pregnancy, post-partum, and menopause have a significant impact on the likelihood of acquiring or worsening autoimmune rheumatic disease outcomes in postmenopausal women with RA. Menopause is frequently associated with the deterioration of chronic rheumatic disease outcomes, which is attributed to the significant decline in the production of gonadal steroids, particularly estrogens, that happens during this phase (Alpízar-Rodríguez et al. 2016; Cutolo & Gotelli 2023). In women, the prevalence tends to gradually increase after the menopause age of 50 years; the prevalence rate has been reported to be 2–2.7% (Yuk et al. 2023). In the general population, the prevalence of RA ranges from 0.5 to 2% (Conforti et al. 2021). In females, hormones play a significant role in the prevalence and progression of RA. Early research compared the prevalence of RA in both women and men, while more recent studies have concentrated on certain reproductive variables and sex hormones, such as estrogens and androgens. However, more scientific research is required for the role of hormones in RA (Alpízar-Rodríguez et al. 2016).. Gonadal hormones, such as estrogen, progesterone, and testosterone, have significant pro-inflammatory and anti-inflammatory effects on the immune system although estrogen has a dual influence on inflammation which may vary depending on the kind of cells primarily engaged in the development and progression of the autoimmune disease. Postmenopausal women may experience a decline in estrogen levels, which affects the progression and severity of RA. This might increase the autoimmune rheumatic disorders that are predominantly influenced by T cells. Androgens have both direct and indirect anti-inflammatory effects on the immune system, which result in suppressing autoimmune rheumatic illnesses in males compared to women (Cutolo and Gotelli 2023; Alpízar-Rodríguez et al. 2016). Research has demonstrated that individuals of both genders having RA have reduced amounts of gonadal androgens (including androstenedione, testosterone, and dihydrotestosterone) and adrenal androgens (such as dehydroepiandrosterone sulfate) in their bloodstream, whereas have a significant elevation in the proportion of estrogen (β Estradiol)to androgens in their synovial fluid (Alpízar-Rodríguez et al. 2016). Hormone level in synovial fluid was noticed that the levels of dehydroepiandrosterone (DHEA) had an opposite relationship with the severity of the condition and are linked to autoimmunity. However, the levels of corticotrophin-releasing hormone (CRH) in both synovial fluid and tissues of individuals with RA remain consistent, independent of steroid therapy (Fernanda Romo-García et al. 2020). Moreover, RA increases the conversion of androgens to estrogens due to inflammatory chemical properties, the activity of aromatase in tissues is enhanced which are not part of the primary organs (Alpízar-Rodríguez et al. 2016). According to Black et al. (2023), it has been found that the prevalence of RA was consistently greater in women than in men across all years of studies. In 2020, the global age-standardized prevalence rate for females was 293.5 per 100,000 population, whereas for males, it was 119.8 per 100,000 and the prevalence of age-standardized females to males ratio, was 2.45 (Black et al. 2023). Thus, this study aims to investigate the impact of different hormones on the development or alleviation of RA, along with evaluating the efficacy of hormonal and complementary treatments in managing RA.

Mechanisms involved in the initiation and progression of rheumatoid arthritis

The cause of RA is still not fully understood, but studies have shown that a combination of genetic and environmental factors contribute to its development where individuals who have a genetic susceptibility as a result of a mixture of environmental factors, genetic variation, and epigenetic modification are triggered suddenly. The abnormal activation of the immune system is stimulated by alterations that occur after protein synthesis, which are influenced by individuals with genetic susceptibility and environmental variables (Alpízar-Rodríguez et al. 2016; Díaz-González and Hernández-Hernández 2023; Lin et al. 2020). It is thought that two separate events play a role in the development of RA. First, the patient has a genetic predisposition that causes autoreactive T and B cells to be produced. Second, antigen-presenting cells (APCs) are activated by a triggering condition, like a bacterial or viral infection or tissue damage, and they present antigens to the cells that were previously created. In RA, synovitis is a condition characterized by inflammation of the joint capsule where the inflammation is caused by autoimmune tissue damage and the ongoing inflammatory environment in the arthritic joint. The synovial membrane,

synovial fluid, and surrounding bones are affected, leading to bone erosion and cartilage deterioration. A key factor in this process is the swelling and invasion of the synovial membrane, known as the "pannus," at the interface between the cartilage and bone (Lin et al. 2020). The pathology of RA is chronic inflammation of the synovium, accompanied by significant thickening of the lining layer and an infiltration of inflammatory cells (Katrib et al. 2002). Synovium serves two main roles in homeostasis—it produces lubricants that enable the cartilage surfaces to operate in a low-friction environment and provide nutrients to cartilage, which is devoid of its blood supply (Smolen et al. 2018). Synovium is characterized by a mixture of bone marrow-derived macrophages and specialized fibroblast-like synoviocytes (FLSs) (Guo et al. 2018). The FLS cell is an essential non-immune cell which is mostly found in the synovium's inner layer and are specialized mesenchymal cells that supply extracellular matrix (ECM) components and nutrition for cartilage (Masoumi et al. 2021). FLSs create a micro-environment that allows for the survival of T cells, B cells, and neutrophil accumulation and its dysfunction leads to hyperplastic synovium, whereas the abnormal proliferation results from a loss of contact inhibition that plays a critical role in RA by producing inflammatory cytokines and proteinases, such as matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) that maintain joint destruction (Guo et al. 2018). MMPs are divided into membrane-type gelatinases, stromelysins, and collagenases based on their substrates. In the development of RA, the collagenases MMP-1, stromelysin, MMP-3, and MMP-13 are more significant. The cartilage's state is determined by the ratio of TIMPs to MMPs. When the ratio of MMPs is increased by inflammatory cytokines such as IL-17, TNF-α, and IL-1β, the cartilage will be damaged which confirms the role of inflammation in joint degradation (Masoumi et al. 2021). The joint inflammation is initiated and maintained by a complex interplay between different dendritic cells (DCs) subtypes, T cells, macrophages, B cells, neutrophils, fibroblasts, and osteoclasts. In RA, T cell is an essential component comprises of Th1 and Th17 T cell subsets which are the predominant cell types found in the inflamed synovial tissue (Lin et al. 2020). Activated T cells in the synovium interact with macrophages, dendritic cells, synoviocytes, and osteoclasts, contributing to RA pathology. Th1 cells secrete IL-2, IFN-γ, and TNF-β, which help other immune cells, activating macrophages together with B cells, initiating, and perpetuating inflammatory responses in the synovium. The macrophage-like synoviocytes produce a variety of pro-inflammatory cytokines, including IL-1, IL-6, TNF-α, IL-17A, IFN-γ, and receptor activator of nuclear factor kappa beta ligand (RANK-L) which play a crucial role in establishing RA inflammation (Smolen et al. 2018). IL-17A produced by Th17 cells contributes to bone erosion, cartilage destruction, and neo angiogenesis in RA patients due to the maturation and activation of osteoclasts (bone-resorbing cells) by receptor activator of NF-κB (RANK; also known as TNFRSF11A) ligand (RANKL; also known as TNFSF11) produced by T cells, TNF, IL-6 and IL-1 formed by macrophages and FLS in the synovial lining (Lin et al. 2020; Smolen et al. 2018). Tumor necrosis factor alpha (TNF-α) is a primary inflammatory cytokine consisting of 157 amino acids that exhibits pleiotropic effects on several cell types and is primarily produced by natural killer cells (NK), T lymphocytes, plus activated macrophages which is detected at elevated levels in individuals afflicted with the condition (Jang et al. 2021). It also induces cartilage degradation and bone resorption, that promotes osteoclastogenesis by enhancing RANK-L secretion by osteocytes RANK-L which is a member of the TNF superfamily and is crucial for bone regeneration and remodelling. (Lin et al. 2020). Moreover, TNF-α-induced osteoclast activation stimulates synovial hyperplasia and angiogenesis, hence contributing to the pathophysiology of RA (Jang et al. 2021).

Additional risk factors for RA include the existence of specific human leukocyte antigens (HLA) alleles, modifications in co-stimulatory pathways (such as alterations in CD28 or CD40 expression), as well as changes in innate immune cell activation, lymphocyte activation thresholds (such as PTPN22), or cytokine signaling (Lin et al. 2020). HLA alleles elevate the risk of RA through several interactions with environmental and other genetic risk factors. The protein structure linked to RA was first identified as a homologous amino acid sequence at positions 69–74 of the beta chain, that was encoded by the HLA-DRB1 gene (Padyukov 2022) which are responsible for around 50% of the genetic vulnerability identified in the development of RA. Furthermore, some HLA-DRB1 variants have been linked to heightened bone degradation and elevated death rates (Lin et al. 2020).

Immune cells, including lymphocytes and monocytes, are drawn actively into the synovial tissue and undergo activation and differentiation. Tissue-specific factors influence the differentiation of monocytes into DCs or macrophages. Due to their capacity to deliver antigens, DC are essential regulators of both innate and adaptive immune responses (Canavan et al. 2020). DCs can be drawn to the site of inflammation by inflammatory cytokines, or they might live within tissues (tissue-resident DCs). Pattern recognition receptors (PRRs), such as cell surface C-type lectin receptors (CLRs), toll-like receptors (TLRs), and intracytoplasmic NOD-like receptors (NLRs), are expressed on DCs and recognize pathogen-associated molecular patterns (PAMPs) (exogenous ligands) or damage-associated molecular patterns (DAMPs) (endogenous ligands) when comes in contact at the site of inflammation. (Brandum et al. 2021). Completely matured DCs produce IL-12 and IL-23, which induce Th17 reactions and

upset the balance between Th1, Th2, and Th17 (Lin et al. 2020). Another important cytokine in the pathology of RA is IFN-γ because it activates monocytes/macrophages and induces the expression of major histocompatibility complex (MHC) class II on the cells. IFN-γ is the only member of type-II interferons and is produced by T cells, B cells, NK cells, DCs, monocytes/macrophages, in addition with neutrophil granulocytes and is crucial for both innate and adaptive immune responses. (Lin et al. 2020; Kato 2020; Sokolova et al. 2021). RA patients have high levels of IFN-γ in plasma, synovial tissue, and synovial fluid. Increased production of CXCL10 by IFN-γ-activated macrophages and monocytes stimulates the production of TNF-α and RANK-L from CD4 + T cells, therefore, promoting osteoclast development. To further encourage autoimmune responses, IFN-γ produced from B cells suppresses regulatory T cells (Tregs) differentiation. Therefore, IFN-γ contributes to the establishment of early inflammation in RA (Kato 2020).

In RA patients, two main types of autoantibodies are found—rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) and the presence of these two autoantibodies defines a patient as having "seropositive" RA (Lin et al. 2020). B cells found in lymphoid follicles and germinal center-like structures that form in inflamed synovium are responsible for the local production of RF in RA (Song and Kang 2010). RF includes IgM, IgG, and IgA immunoglobulins that target the IgG Fc-fragment (Sokolova et al. 2021). The majority of RF species in RA are IgM RFs, which are seen in 60–80% of RA patients (Song and Kang 2010; Sokolova et al. 2021).

New autoantibodies known as ACPAs are present in 70–90% of RA patients and have a high clinical specificity of 90–95%. Generally, ACPA is more sensitive and specific than RF when it comes to diagnostic value. They are linked to more erosive RA, just like RF (Song and Kang 2010). In RA, ACPA can induce pain, bone loss, and inflammation. The environment serves as a trigger for the creation of ACPAs, which are detectable long ahead of joint symptoms. Up to 10 years before clinical disease manifestation, circulating pro-inflammatory cytokines, chemokines, and other antibodies (such RF and ACPAs) have all been found to be indicative of immune activation during the preclinical phase (Guo et al. 2018). ACPA bind to proteins that contain citrullinated epitopes, such as vimentin, α-enolase, type II collagen (CII), fibrinogen, fillagrin, fibronectin, and immunoglobulin-binding protein (BiP), among others however its interaction with citrullinated peptides expressed by osteoclast and its precursor cause osteoclast maturation and activation, (Sokolova et al. 2021; Smolen et al. 2018). It can enhance nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) activity and TNF-α production in monocyte/macrophages via binding to surface-expressed citrullinated Grp78.52 α-Enolase on the surfaces of monocytes and macrophages induces production of pro-inflammatory mediators (Guo et al. 2018). Figure 1 represent the mechanism onset of rheumatoid arthritis.

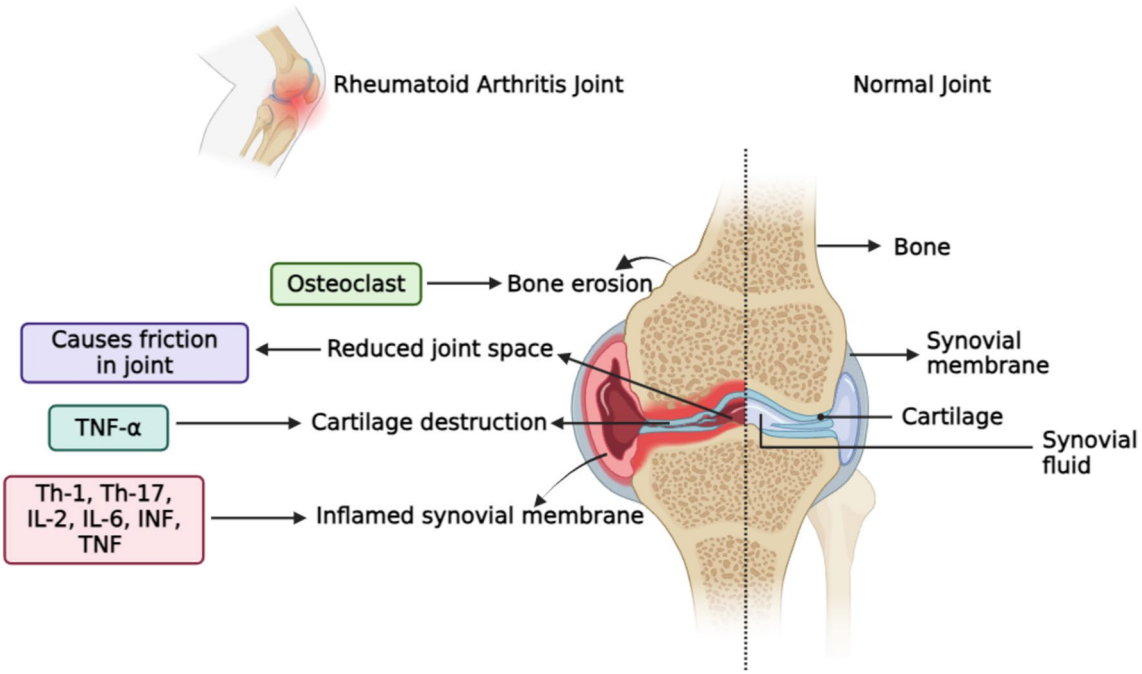

Fig. 1 Mechanism of onset of rheumatoid arthritis

Effects of sex hormones on rheumatoid arthritis

Estrogen

These are steroid molecules that originate from cholesterol. There are four types of estrogens that have been identified: 17β-estradiol (E2), Estrone (E1), Estriol (E3), and Estetrol (E4), its impact and working in rheumatoid arthritis as shown in Fig. 2. In females, the hormone estradiol (E2) is produced in the ovaries from the onset of puberty until the onset of menopause. E2 plays a crucial role in the development of both primary and secondary sexual characteristics in women. However, it is also created in men through the process of aromatization, where testosterone is converted into estradiol. Approximately 20% of estradiol production in males occurs in the testes, while the remaining 80% takes place in peripheral tissues (Noirrit-Esclassan et al. 2021). Estrogens have a crucial role in regulating skeletal growth, maintenance and have several physiological effects, such as promoting the development plus maturation of the reproductive system, skeleton, immunological, neurological, and cardiovascular systems (Islander et al. 2011). The association between immune response and estrogens in RA was initially discovered by S. Hench in 1938. Hench observed that pregnancy improved symptoms of RA, leading him to propose a hypothesis that hormone deficiency could contribute to the development of RA. Moreover, adrenal insufficiency was responsible for the pathogenesis of RA (Fernanda Romo-García et al. 2020). In normal amounts, estrogens generally boost immunological responses and can play a significant role in stimulating human humoral immunity (Cutolo et al. 2004). Estrogen exerts both stimulatory and inhibitory effects on the immune system and has an impact on cells belonging to both the innate and adaptive immune system (Alpízar-Rodríguez et al. 2016); Islander et al. 2011). According to epidemiological and immunological assessments, estrogens possess anti-inflammatory effect on T cells whereas pro-inflammatory effect on B cells, at high concentration by by inhibiting TH1 and TH17 cells via estrogen receptor-α and often boost the immune response of B cells in humans, but also appear to have significant involvement in the development of autoimmune rheumatic disorders (Cutolo et al. 2012; Cutolo and Gotelli 2023). On macrophages and monocytes, estrogen has a dual-enhancing impact that can be either pro- or anti-inflammatory. The high levels of estrogen suppress the production of pro-inflammatory cytokines while encouraging Th2 responses and humoral immunity whereas low levels of estrogen increase the

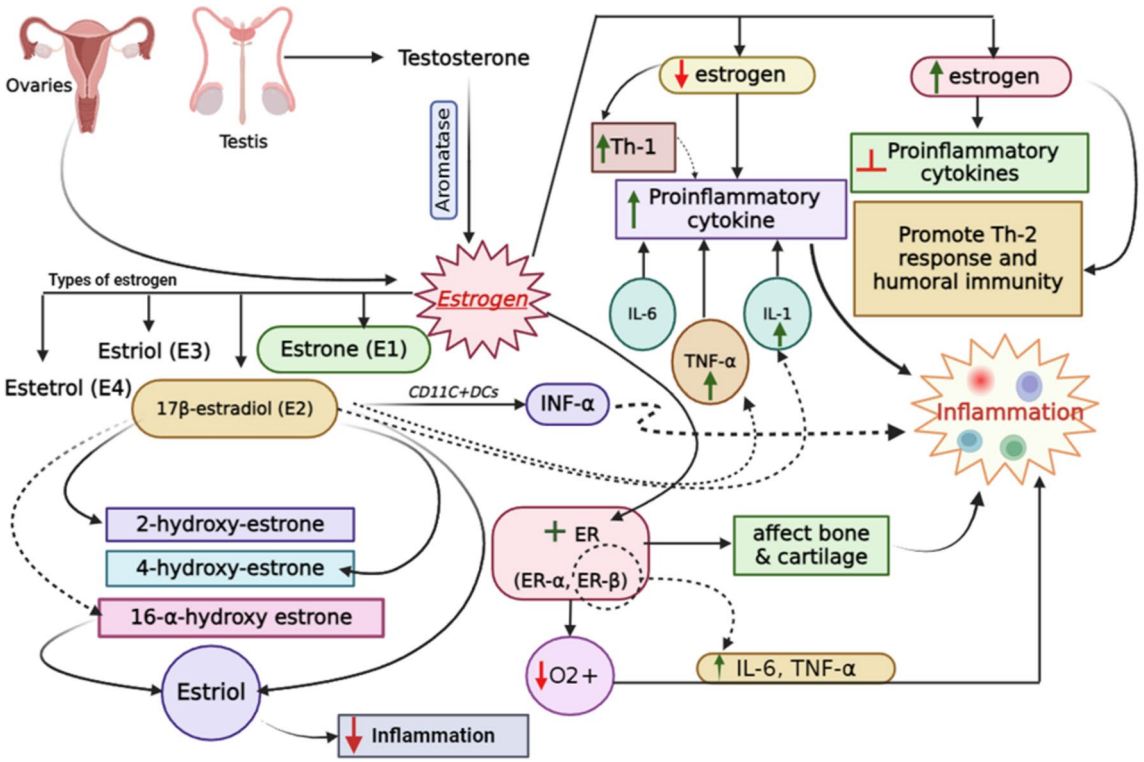

Fig. 2 Impact and functions of estrogen concerning the occurrence of Rheumatoid Arthritis

production of pro-inflammatory cytokines (IL-1, IL-6, and TNF-α), Th1 responses, and cellular immunity (Shen et al. 2023). The elevated levels of estrogen in the synovial fluid of individuals with RA are mostly composed of hydroxylated forms, specifically 16α-hydroxyestrone and 4-hydroxyestradiol. Additional derivatives of E1 and E2 involve 2-hydroxylated estrogens, including 2-hydroxyestrone and 2-hydroxyestradiol. According to research, 16α-hydroxyestrone a cell proliferative hormone together with 16alpha-hydroxy-17beta-estradiol, is responsible for inhibiting monocyte proliferation (Cutolo et al. 2012). A recent study revealed that the urine levels of 2-hydroxylated estrogens were significantly lower in patients with RA compared to healthy individuals. Additionally, the ratio of 16α-hydroxyestrone to 2-hydroxyestrogens was shown to be much greater in RA patients, with a 20-fold increase compared to the control group. The decrease in 2-hydroxylatedestrogens compared to the mitogenic 16α-hydroxyestrone may play a crucial role in promoting the proliferative state of synovial cells in RA (Cutolo et al. 2004). Estrogens have the ability to influence several immune cells, producing different effects on each specific cell type (such as T cells, B cells, NK cells, DCs, etc.). Estrogen binds to estrogen receptors (ER-α and ER-β) in the synovial tissue of persons with RA and transmits its effects on bone and cartilage. As a result, there is a reduction in the delivery of oxygen and an elevation in the level of inflammation. Estrogen receptor-β (ER-β) expression plays a function in both promoting inflammation and raising the production of Interleukin-6 (IL-6) as well as TNF-α by surrounding mononuclear cells. (Cutolo et al. 2012; Cutolo 2000). During the conventional transcription route, estrogen receptors (ERs) attach to estrogen molecules, combine to form a receptor dimer, and go into the nucleus of the cell. At that location, they combine with co-regulatory proteins and attach to the estrogen response elements (EREs) in order to start the process of transcription. The EREs are located in the promoter regions of many genes that are under the control of estrogens. In the non-classical transcription route, the estrogen/ER complex initiates transcription by attaching itself to alternative transcription factors such as AP-1, SP-1, and NFB, which bind to locations other than ERE. (Islander et al. 2011; Cutolo et al. 2003). E2 attaches to ERs, which are found in diverse tissues with varying distribution. E2 is synthesized by the granulosa cells of the ovary, as well as to a lesser extent by the adrenal cortex, adipose tissue, and testicles, through the process of aromatization of testosterone. E2, E1, and other hydroxylated metabolites derived from them have been observed to be considerably elevated in the synovial fluid of both male and female patients with RA. This rise is attributed to the excessive production of aromatase enzymes inside the affected cells (Alpízar-Rodríguez et al. 2016; Islander et al. 2011; Cutolo et al. 2012). E2 was observed to stimulate the production of CD40, a costimulatory molecule that plays a vital function in regulating the immunological response of effector cells, in DCs through the activation of p38 and mitogen-activated protein kinase (MAPKs). Recent studies have shown that estrogens can increase the production of MMPs, and IL-1β-induced IL-6 release in human fibroblast-like synoviocytes in RA. Moreover, the use of anti-estrogens prevented the transformation of synovial fluid macrophages into DCs and hindered the ability of synovial fluid macrophage-derived DC to activate allogeneic T cells (Cutolo et al. 2012). Estrogens also support Tregs and TH2 cell-associated cytokines production. (Cutolo and Gotelli 2023). Estrogen influences bone through direct effects on cell types and changes in the cytokine environment of bone (Islander et al. 2011). In RA patient, the expression of osteoprotegerin (OPG) is stimulated by estrogen and is not controlled by progesterone whereas, variety of substances, including glucocorticoids, vitamin D3, IL-1, IL-6, IL-11, IL-17, TNF-α, and PTH, enhance the production of RANKL. Estrogen insufficiency can result in increased bone resorption due to the excessive expression of RANKL on bone marrow stromal cells. Estrogen has an impact on the levels of TNF-α and IL-1. Additionally, estrogen treatment has been found to prevent the increase in sIL-6R levels that occurs after ovariectomy. (Forsblad d'Elia and Carlsten 2006). Moreover, CRH maintains a consistent presence in synovial fluids and tissues, even when steroid treatment is administered (Cutolo et al. 2004).

Androgen

There are four androgen hormones, namely dihydrotestosterone (DHT), testosterone (T), androstenedione (ASD), and dehydroepiandrosterone (DHEA), which are all produced from cholesterol in the gonads and adrenal glands. Out of the four androgens, only DHT cannot be transformed into estrogens. Therefore, research that uses DHT is the most straightforward to analyze. Adrenal (ASD & DHEA) and gonadal androgens (T & DHT) have anti-inflammatory characteristics by inhibiting the release of pro-inflammatory substances such as IL-1β, IL-6, TNF, etc. (Gubbels Bupp and Jorgensen 2018; Schmidt et al. 2005). The direct and indirect anti-inflammatory effects of androgen lead to a lower risk of developing autoimmune rheumatic diseases in men compared to women. Specifically, individuals with RA have been found to have reduced levels of gonadal androgens and adrenal androgens in their body fluids, such as blood, synovial fluid, smears, and saliva. Additionally, the androgen/estrogen ratios in these patients are also lower. (Cutolo et al. 2002; Cutolo and Gotelli 2023). Testosterone is the predominant androgen found in the bloodstream of adult

males. On average, men who had early RA have decreased levels of bioavailable testosterone and female patients with active illness have exhibited low amounts of testosterone in their synovial fluids (Gubbels Bupp and Jorgensen 2018; Schmidt et al. 2005). During chronic inflammatory processes like active RA, the activation of the hypothalamus–pituitary–adrenal axis by pro-inflammatory stimuli can result in decreased levels of serum testosterone and DHEAS. This occurs because testosterone is converted into estrogen. It is widely recognized that there is a relationship between blood testosterone levels and the activity of RA. Additionally, the levels of DHEAS are negatively associated with both the length and severity of the disease. It is worth noting that testosterone, along with its precursors DHEAS and DHEA, possess anti-inflammatory characteristics. TNF antagonists enhance adrenal function by elevating levels of DHEAS in individuals with active RA (Gubbels Bupp and Jorgensen 2018; Schmidt et al. 2005; Cutolo 2009). The androgen receptor (AR) also plays an important role in immune function by modulating the transcription of genes through DNA-binding-dependent and independent mechanisms. Both monocytes and macrophages exhibit the presence of both classical and non-classical AR (Gubbels Bupp and Jorgensen 2018). Human macrophages possess essential enzymes involved in steroidogenesis, enabling them to convert testosterone into DHT. The rate and quantity of testosterone conversion into DHT in human macrophages is equivalent to target cells for androgen action, such as human prostate cancer cells. Testosterone at both physiological and pharmacologic levels suppresses the release of IL-1β by PBMCs derived from individuals with RA. Testosterone at normal levels also suppresses the production of IL-1 in human synovial macrophages and reduces monocyte IL-6 production but does not directly affect isolated B or T cells. (Cutolo et al. 2002). IL-6 can decrease adrenal androgen output in males, leading to low blood androgens in some situations (Gubbels Bupp and Jorgensen 2018). When androgen concentrations are low, there is no suppression of the local mononuclear cells that produce inflammatory cytokines such as IL-6 and TNF-α (Cutolo 2000). Testosterone can suppress the release of cytokines, including TNF and IFN- ϒ, from activated leukocytes in human peripheral blood. The presence of inflammatory cytokines, such as IL1β and TNF, leads to a decrease in androgen levels by inhibiting the enzyme cytochrome P450c17, which affects both adrenal and gonadal androgen production (Cutolo 2009).

Androgens can inhibit both humoral and cellular immune responses and appear to function as natural hormones that reduce inflammation (Cutolo et al. 2002). According to a study, hormone receptor genes and plasma androgens do not play a role in the development of RA in females. It also suggests that individuals with active RA experience disruptions in peripheral androgen metabolism and the regulatory influence of estrogens (Cutolo 2009). The development of lymphoid cells (T cells, B cells, and natural killer cells) is directly influenced by androgens. After exposure to androgens, these lymphoid cells maintain their characteristics, even when placed in an androgen-depleted environment. These findings indicate that the presence of androgens can have a lasting effect on the growth and function of these cells, resulting in a reduction of inflammation in patients with RA (Cutolo et al. 2002; Gubbels Bupp and Jorgensen 2018). Figure 3 represent the specific role of androgen in the prevalence of rheumatoid arthritis.

Progesterone

It is a naturally occurring steroid hormone that is primarily synthesized by the adrenal cortex and the gonads, which include the ovaries and testes. Progesterone is produced by the ovarian corpus luteum in the initial ten weeks of pregnancy and later by the placenta throughout the latter stages of pregnancy (Cable JK and Grider MH 2021). It is an immunoregulatory hormone that suppresses the immune system and has an unknown impact on the immunological pathways associated with RA as shown in Fig. 4. Progesterone exerts its influence on cellular function by direct interaction with membrane-bound and intracellular (cytosol and nuclear) receptors, triggering signaling cascades (Cutolo 2000). Progesterone exerts extensive anti-inflammatory effects by inhibiting activation-induced cytidine deaminase (AID), TH1, and TH17 immune responses, as well as the activity of NK cells, neutrophils, and macrophages. It also stimulates the TH2 immune response by increasing the production of IL-4 and IL-10 in human T cells (Raine and Giles 2022). When progesterone is administered during pregnancy, RA can be less harmful and inflammatory. By lowering the amounts of reactive oxygen species (ROS) and apoptosis, it prevents neutrophil activity, which may cause joint injury. Furthermore, it lessens inflammation and damage by reducing the synthesis of IFN-γ in NK cells. Additionally, progesterone inhibits macrophages' synthesis of TNF-α and nitric oxide, which may help to lessen the symptoms of RA during pregnancy. DCs produce more progesterone than pro-inflammatory cytokines, resulting in lower pro-inflammatory cytokines and making it easier for Tregs and Th2 cells to present antigens. Furthermore, progesterone reduces chronic inflammation by blocking TLR-9 signalling, which decreases the production of IFN-α in plasmacytoid DCs. It also controls the responses of CD4 + T cells by encouraging the growth of Th2 cells, blocking the development of Th1 and Th17 cells, and encouraging the differentiation of Treg cells (Cutolo 2000). During pregnancy, due to the involvement of Tregs, the Th2 response is strong in comparison to the TH1 immune response. The symptoms of RA often show improvement during pregnancy, maybe

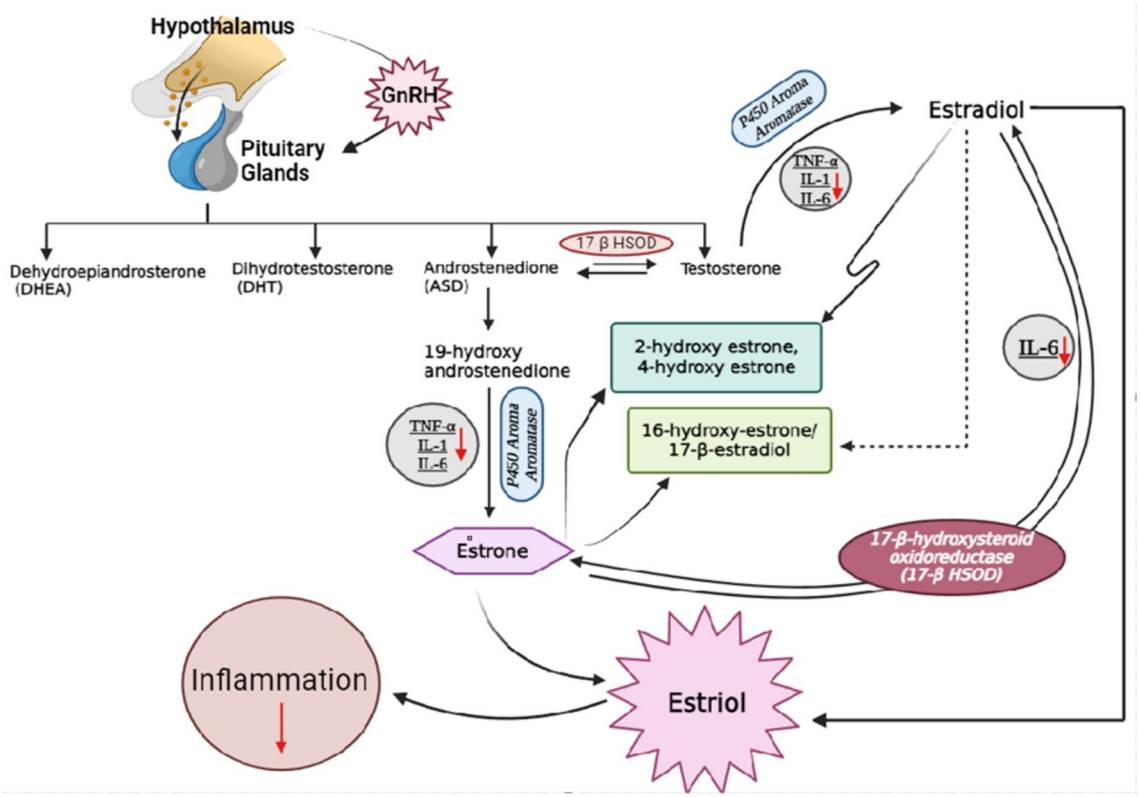

Fig. 3 The Role of Androgens in the Prevalence of Rheumatoid Arthritis

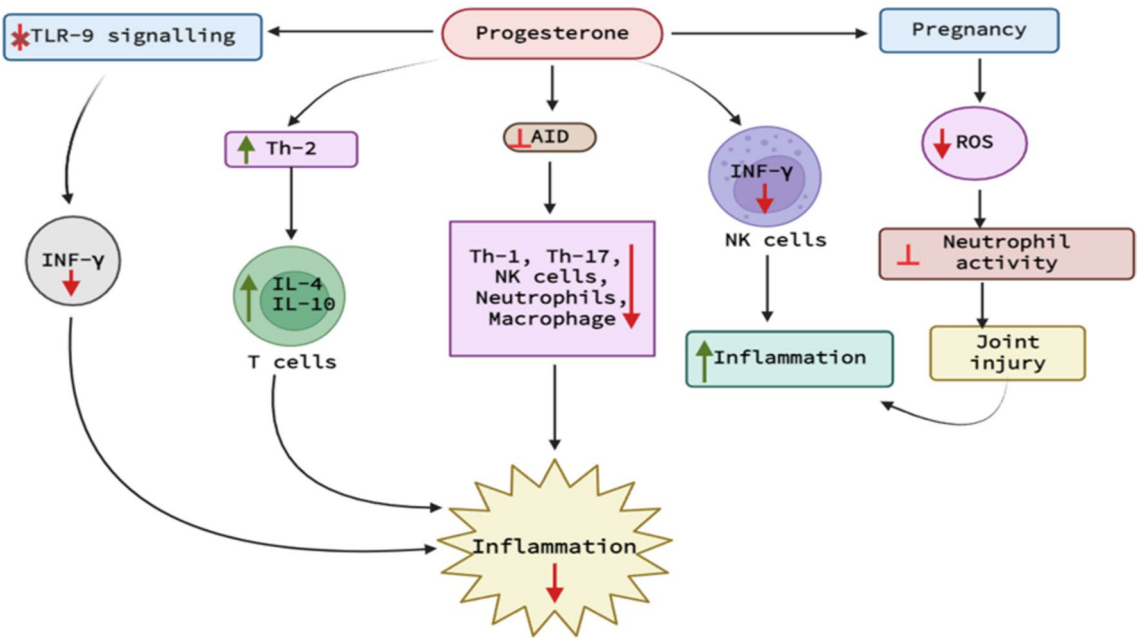

Fig. 4 Exploring the impact of progesterone on rheumatoid arthritis

because of reduced numbers of Th17 cells in the third trimester in comparison to women who are not pregnant (Tan et al. 2015). It also encourages the formation of Tregs from human fetal cord blood T cells and prevents their differentiation into TH17 cells. During pregnancy, lymphocytes express receptors for progesterone and produce a substance called progesterone-induced blocking factor, which has a powerful inhibitory effect on NK cells. Additionally, they also secrete interleukin-10 (IL-10). Progesterone inhibits the activation of CD4 + T cells in healthy human females in a manner that depends on the dosage. This inhibition leads to major alterations in the expression of genes and pathways associated with the immune system, including the downregulation of signal transducer and activator of transcription-1 (STAT-1) and signal transducer and activator of transcription-3 (STAT3), which are crucial in RA (Raine and Giles 2022). It is considered that pregnancy and oral contraceptives can guard against the development of RA, perhaps delaying or altering the progression of the illness rather than offering complete protection (Tan et al. 2015). Pregnancy-level estrogen administration prior to collagen immunization reduces the development of the disease in animal models of RA, such as collagen-induced arthritis (CIA), by lowering responses to prostaglandin E2 (PGE2), TNF-α, IFN-γ, and anti-collagen antibodies. Pregnancy-related RA remission may be caused by Progesterone-induced alterations in systemic immune activities, including elevated IL-1RA, Tregs induction, inhibition of Th1 or Th17 responses, increased Th2-related responses, and elevated terminal galactose residues on circulating Ig (Hughes 2012).

Effect of menopause on RA

RA predominantly impacts females and presents as bilateral inflammation and sensitivity in several joints. Menopause, the natural cessation of menses in women typically occurring between 45–60 years of age, resulting in decreased ovarian sensitivity to gonadotropin stimulation, leading to systemic changes (such as increased cardiovascular risk, decreased bone density, and mood disturbances) due to decreased estrogen and progesterone levels (Shah et al. 2020). Onset and progression of chronic autoimmune diseases like RA are more common in women, correlated with aging and menopause, characterized by hypo-estrogenaemia, osteoporosis, hot flashes, vaginal dryness, mood disorders, and cardiovascular disease with hormone replacement therapy being a common treatment option (Cutolo and Gotelli 2023; Shah et al. 2020). Early menopause (EM) < 44 years is associated with an increased risk of developing RA and is mainly associated with seronegative RA (Cutolo & Gotelli 2023). Menopause has been allied with the development of ACPA in first-degree relatives of RA patients (Tan et al. 2015). Although it is more commonly associated with decreased production of estrogen, progesterone and androgens such as DHEA, DHEAS, ASD, and testosterone. In RA patients, both corticosteroids and testosterone levels were considerably reduced throughout both the luteal and follicular phases whereas in women a notable decline in progesterone levels during luteal phase was observed (Kanik and Wilder 2000; Cutolo and Gotelli 2023). The decline in gonadal steroid synthesis, namely estrogens, after menopause, often leads to the worsening of rheumatic disease outcomes. (Cutolo and Gotelli 2023). Menopause affects the synthesis of cytokines, resulting in increased levels of IL-1, IL-6, TNF, and M-CSF (macrophage colony-stimulating factor) after menopause. Nevertheless, the administration of estrogen therapy leads to a drop in these levels. Cytokines influence the function of osteoblasts and osteoclasts leading to bone loss. IL-6 has pro-osteoporotic properties, and its levels can be used as a predictive marker for bone loss in postmenopausal women. Menopause leads to an increase in the levels of the soluble IL-6 receptor. The soluble IL-6 receptor acts as an immune stimulant by attaching to IL-6 and interacting with the identical signal transduction pathways as the receptor located on cell membranes. Hormone replacement treatment can prevent and reverse this rise (Islander et al. 2011). Figure 5 represent the effects of menopause in rheumatoid arthritis. The diminished immunomodulatory effects of estrogens after menopause may potentially contribute to worse clinical outcomes in people with RA, whereas the rise in estrogen levels during pregnancy is known to provide a protective effect against disease flares in individuals with RA, resulting in reduced disease activity at the start of pregnancy (Cutolo and Gotelli 2023). During pregnancy, women have a decrease in their vulnerability to RA due to an increase in the quantities of estrogen, progesterone, and corticosteroids in their bloodstream (Forsblad d'Elia and Carlsten 2006). Table 1 represent the in vivo and in vitro model studies on hormonal effect on RA.

Hormonal therapies for RA

Hormone therapy is the application of hormones or hormone antagonists in medical treatment. This treatment has the ability to manipulate hormones by either adding, blocking, or eliminating them. Treatment for decreased hormone levels in individuals with specific illnesses, such as menopause or diabetes, involves hormone replacement therapy (HRT). (Definition of Hormone Therapy—NCI Dictionary of Cancer Terms – NCI). There have been studies conducted on two types of hormonal therapies, namely HRT and selective estrogen receptor modulators (SERMs), to examine their potential effects on RA. In addition, there is a new treatment option for RA called gonadotropin-releasing hormone therapy (GnRH). Hormonal therapy can be administered through various methods, such as injections, patches, oral

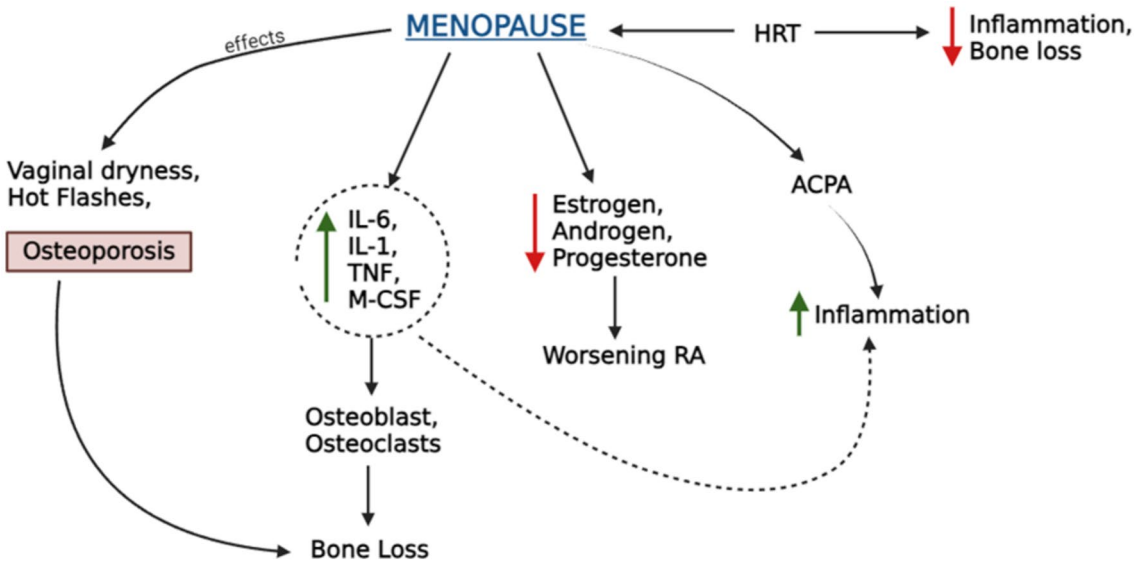

Fig. 5 Effects of menopause in rheumatoid arthritis

pills, and more. While generally considered safe, certain therapies can have potential side effects such as changes in mood, hot flashes, and nausea (Hormone Therapy for Cancer – NCI; Harper-Harrison et al. 2024). Some of the therapies are mentioned below:

Hormone replacement therapy (HRT)

It is supplementing women with hormones that are lost during the menopausal transition. It includes treatment that combines progestogen with estrogen to protect the endometrium in women which is present in their uterus and alleviates menopausal symptoms (like vaginal dryness, mood swings, hot flashes, and night sweats) and physical changes brought on by low endogenous estrogen levels. When HRT is initiated after the age of 60, it preserves spinal bone density and guards against hip fractures caused by postmenopausal hip dysplasia (Harper-Harrison et al. 2024; Burkman et al. 2001; Hickey et al. 2012; Levin et al. 2018). HRT in RA improves disease activity, articular index, pain scores, and bone health, potentially shielding against joint destruction in postmenopausal women and rising BMD even in those patients on Gluccorticosteroid therapy (Forsblad d'Elia and Carlsten 2006). HRT has evolved with different perspectives on its benefits and risks, it began popular for reducing osteoporosis, coronary artery disease, and mortality, but was later considered differently as Women's Health Initiative (WHI) study reported increased risk of coronary diseases and breast cancer associated with HRT; however, subsequent reanalysis of WHI data, along with newer studies, suggests that initiating HRT close to menopause onset can reduce coronary heart disease and mortality (Lobo 2017). HRT was initially promoted as a means for women to overcome the effects of estrogen loss and maintain their femininity, with the Food and Drug Administration (FDA) approving HRT in 1988 for the prevention of osteoporosis in addition to its initial approval for the treatment of hot flashes (Cagnacci and Venier 2019). During a study conducted in the 1980s and 1990s, researchers examined the impact of HRT containing estrogen alone or a combination of estrogen and progesterone suggesting that HRT had an anti-inflammatory effect. There are various types of HRT used in the treatment of RA, including estrogen therapy (estradiol, estradiol 17β, estrone, or conjugated equine estrogen (CEE)), androgen, and testosterone therapies. Estrogen can be applied using different methods including topical, intravaginal, or oral administration. Similarly, progestogen can be administered through intraperitoneal, transdermal, or oral routes. Research on androgen therapy, specifically testosterone administration, has yielded varying outcomes when it comes to disease activity and BMD. (Forsblad d'Elia and Carlsten 2006) Estrogen replacement therapy has been associated with improvements in bone density, decreased risk of osteoporotic fractures, and the suppression of TNF-α, IL-1, and IL-6 production by macrophages. (Harper-Harrison et al. 2024). In another study conducted by D'Elia et al. (2003), postmenopausal women with active RA were given HRT consisting of micronized E2 and noretisterone acetate. They were also treated with calcium and vitamin D3 where the results showed significant reductions in inflammation, as evidenced by a decrease in erythrocyte sedimentation rate (ESR), and an increase in hemoglobin concentration. In addition to its

Table 1 In vivo and In vitro studies on hormonal effect on RA

Hormone	Model/dose	Mechanism	Results	Study
Estrogen	B10.RIII mice Dose: 3.2 µg E2 (17β- estradiol-benzoate)/olive oil 50 µg E3 (estriol-benzoate)/olive oil	Decreased the levels of autoantibodies to type II collagen in the blood Indicating a reduction in the autoimmune response It also lowered the activity of pro-inflammatory cytokines in T-cells	Blocking the development and onset of the disease RA	Jansson L et al. (1994)
Estrogen	Female DBA/1 mice Dose: 0.83 µg of E2 per mouse	The disease development was postponed Decrease in the quantity of TH17 cells and neutrophils in the joints The administration of E2 also results in a decrease in the quantity of IL-17-producing cells The reduction in the number of neutrophils present in the joints	Decreasing the severity and incidence of arthritis	Andersson A et al. (2015)
Androgen (Testosterone)	Male and Female Wistar rats Dose: Dihydrotestosterone (DHT) of 25 mg	DHT suppresses the immune response Reduced the levels of the proinflammatory mediator, PGE2 It also suppressed the inflammatory cytokines T and B cells Exhibit an anti-inflammatory effect	Reduction in inflammation, edema volume, and joint erosion	Ganesan K et al. (2008)
Progesterone	DBA/1 mice a) Dose: 3.2µg 17-β estradiol-benzoate in a volume of 0.1 ml olive oil b) progesterone + estrogen	Estrogen suppressed arthritis by reducing T-cell mediated reactivities against anti-type II collagen Developed a suppressed IgG autoantibody response	Delayed onset of arthritis	Jansson L et al. (1989)

other benefits, HRT has been found to improve BMD in the forearm, proximal femur, and spine. It has also shown promise in slowing down the progression of joint destruction in patients with radiologically progressive disease (D'Elia et al. 2003). Male patients with RA who received testosterone undecanoate experienced a notable reduction in the CD4 + CD8 + ratio, ESR, concentration of IgM-RF (immunoglobin G–rheumatoid factors), tender joints, and daily Nonsteroidal Anti-Inflammatory Drug (NSAID) dosage. The study indicates that testosterone therapy has a beneficial effect on immune response and the ratios of T cells. Emphasizing the potential advantages of androgen replacement therapy in managing RA (Cutolo et al. 1991). According to a study conducted by Hall et al. (1994), it was found that postmenopausal women with RA experienced positive effects when treated with a combination of estradiol and norethisterone. The study concluded that patients who received HRT had higher BMD, with the mean lumbar spine BMD improving by more than 2% after 2 years. However, the femoral BMD showed little change in comparison.

Selective estrogen receptor modulators (SERMs)

These are a varied group of substances that have the ability to bind to ERs and cause a distinct change in the receptor's structure, leading to specific effects in estrogen-responsive tissues. (Gómez-Coronado et al. 2021). SERMs are now being used as a treatment for breast cancer, osteoporosis, and postmenopausal symptoms, as these drugs have features that can act as an estrogen agonist (bone, liver, and Cardiovascular system) and an antagonist (breast and brain), depending on the target tissue (An 2016). Tamoxifen and raloxifene are examples of SERMs; after these two, lasofoxifene and bazedoxifene SERMs have been developed for the treatment. These SERMs mimic the effects of estrogen

in some tissues while blocking them in others. (An 2016; Dodge and Richardson 2007). Developed in the 1970s, tamoxifen is a first-generation breast cancer medication now indicated for ER + (estrogen receptor-positive) breast cancer. Tamoxifen functions as an agonist on bone tissue, maintaining BMD in postmenopausal women, but acting as an antagonist on breast tissue and was also considered for the treatment of osteoporosis. In postmenopausal women, raloxifene a second-generation osteoporosis drug decreases bone loss and guards against vertebral fractures. ER and their modulation of paracrine osteoblastic factors mediates the effects of raloxifene on the skeleton. Human osteoblasts that are exposed to raloxifene produce more OPG which causes bone resorption and less IL-6. (Viereck et al. 2003). Similar to raloxifene, bazedoxifene is a third-generation medication that has also been created to treat osteoporosis (An 2016). In the context of autoimmune illnesses, SERMs have been shown to support anti-inflammatory signaling and immune cell phenotype, particularly macrophages. By promoting M2-type features in macrophages, SERMs can lower inflammation, perhaps mitigating the severity of autoimmune diseases. Because SERMs alter the immune cell activity, they offer a targeted approach to controlling the progression of the autoimmune disease without the negative side effects of traditional steroid hormone therapy (Polari et al. 2018).. The action of SERMs on the ER influences bone homeostasis in relation to osteoporosis and bone loss by decreasing bone resorption and downregulating osteoclast activity in a growth factor-β3-dependent way. Osteoporosis can be prevented and treated because to this effect (An 2016). Raloxifene hydrochloride is a nonsteroidal benzothiophene that binds to estrogen receptors in postmenopausal women and reduces bone resorption without activating the uterine endometrium. When compared to a placebo, raloxifene dramatically raised BMD at the hip and spine and decreased the incidence of vertebral fractures during 3-year period (Ettinger 1999). Also, Lasofoxifene decreased the incidence of both vertebral and non-vertebral fractures while noticeably raising BMD at the hip and spine. It was also linked to a lower chance of coronary events and breast cancer (Cummings et al. 2010).

Gonadotropin-releasing hormone (GnRH) therapy

Half a century ago, the structure of GnRH was identified as a decapeptide (pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly·NH2) following its isolation from pig hypothalami. This peptide was initially documented in scientific literature as the "Luteinizing Hormone-Releasing Hormone (LH-RH)". However, in more recent literature, it has been commonly referred to as the "Gonadotropin-Releasing Hormone (GnRH)," suggesting its role in stimulating the production of both LH and FSH (Marques et al. 2000). GnRH is synthesized in the hypothalamus, which regulates the release of FSH and LH in animals, has a highly conserved molecular structure (Walker and Jacobson 2000; Kass et al. 2015). In both sexes, pituitary LH and FSH induce gonadal hormones, which in turn are activated by GnRH implying that gonadal hormones may be involved in pathogenic processes in both sexes and serve significant physiological roles in both male and female reproduction (Kass et al. 2014). GnRH, which interacts with T cells and regulates the immune response, is also produced by peripheral CD4 + and CD8 + T cells (Walker and Jacobson 2000; Kass et al. 2014). Reduced activity of the RA illness is linked to hypothalamic–pituitary–gonadal axis suppression, which can happen during pregnancy or fasting. On the other hand, when this axis is activated, as it is during the menopausal transition, postpartum, anti-estrogen therapy, or Polycystic ovary syndrome (PCOS), RA symptoms may manifest or intensify. A recent study explored the potential of cetrorelix treatment in patients with high gonadotropin levels in RA. The findings revealed promising results, indicating that short-term GnRH-antagonism had rapid anti-inflammatory effects and improved disease parameters. Additional research is required to gain a comprehensive understanding of the potential of GnRH antagonists in RA and other autoimmune diseases, particularly in specific groups of patients (Kass et al. 2015). A study was conducted on RA patients using Cetrorelix, a GnRH antagonist. It has a notable impact on reducing TNF-α levels. More patients who used cetrorelix showed improved ACR20 responses and lower DAS28-CRP values (< 2.6). After the treatment was stopped, the inflammatory indicators went back to their original values. Both groups experienced similar adverse occurrences. It suggests that cetrorelix and similar GnRH antagonists have the potential to reduce inflammation in RA (Kass et al. 2014).

Complementary/alternative medicine (CAM)

Patients with chronic rheumatic disorders have been increasingly turning to complementary and alternative medicine (CAM) as a means of managing their long-term conditions. In previous studies on arthritis, the prevalence of CAM ranged from 33 to 90% (Kocyigit et al. 2022). Alternative therapies such as acupuncture, dietary changes, herbal medicine, homeopathy, massage, and supplements have shown promising results in the treatment of RA (Andersson et al. 2015; K. Ganesan et al. 2008). Here are a few of them:

Yoga

The Sanskrit term "yoga" has its roots in the concept of joining or binding together, as well as concentration. The concept of "yoga" has evolved to encompass a method of self-control and a means of harmonizing the mind, body,

and soul, or the integration of the individual self with the higher self (Garfinkel and Schumacher 2000). The meditative aspects of yoga have been found to have a positive impact on the parasympathetic nervous system, resulting in a reduction in inflammation (Ye et al. 2020). Practicing yoga can enhance blood circulation to the muscles, leading to improved oxygenation of the tissues. This activity enhances muscle strength, promotes balance, and preserves joint mobility through the maintenance of muscle contraction. Yoga has shown promising results as a therapeutic option for rheumatic disorders as it focus on pain management and depression treatment which is closely linked to its ability to stimulate the vagus nerve, which is believed to contribute to reducing pro-inflammatory cytokines like IL-6, interleukin-2, and C-reactive protein. (C. McCall 2013). The yoga asanas sukshmavyayama and sthoolvyama are great for warming up the small joints of the hands and feet. Trikoṇasana helps to maintain spinal flexibility and strengthen the muscles in the calves, thighs, and waist, which can improve lung capacity. On the other hand, Gomukhasana targets the gluteal muscles, provides relief for knee pain, and helps to develop the spine and abdominal muscles. (Gautam S et al. 2021). In a recent study, Ganesan et al. (2020) examined the potential benefits of yoga by conducting a trial on individuals with RA. The aim was to assess the impact of yoga therapy on their condition. Participants were split into two groups: the yoga group and the control group. Both groups experienced a decrease in disease activity after 12 weeks, but it was evident that the reduction in the yoga group was more pronounced. Within the yoga group, there was a notable decrease in the levels of cortisol and IL-1α. Furthermore, the group practicing yoga showed a positive shift in sympathovagal balance, as evidenced by the heart rate variability measurements. Hence, it has been concluded that the practice of yoga therapy has demonstrated significant improvements in autonomic function and the management of illness in patients with RA (S. Ganesan et al. 2020). A study conducted by Ebnezar et al. (2012) found that yoga can enhance the physical function and grip strength of individuals with RA. It is crucial for people with RA to enhance their muscle strength, balance, and coordination in order to maintain their physical function. These can be accomplished through various yoga postures and exercises. Yoga enhances the expression of genes involved in DNA repair and helps restore the balance between pro- and anti-inflammatory cytokines. By modulating the immune system, it reduces acute-phase reactions and brings inflammatory marker levels back to normal. In combination with Disease-modifying antirheumatic drugs (DMARDs), yoga-based therapies have been found to reduce disease activity in conditions such as RA (Gautam S et al. 2021).

Massage

In nations with limited and moderate resources, alternative therapies like massage therapy provide a more convenient and cost-effective option compared to pharmaceutical and medical interventions (Sahraei et al. 2022). Massage therapy is a well-established method that effectively reduces pain, muscle spasms, and improves overall well-being. It provides immediate relief and offers significant benefits in terms of pain reduction, fatigue reduction, improved sleep, and overall quality of life. Massage therapy involves the manipulation and mobilization of soft tissue and joint structures using hands or a hand-held tool (Tam et al. 2007). Massage has been found to stimulate nerve fibers, resulting in a reduction in pain perception.. In addition, it is believed that massage can enhance the body's production of endorphins, which are natural chemicals that help alleviate pain. This can potentially result in a reduction of chronic pain. Finally, through its various benefits such as reducing muscle cramps, improving joint flexibility, and preventing joint dryness, massage has been found to effectively alleviate pain in individuals. Swedish massage is a therapeutic treatment that focuses on the manipulation of joints through various motions, such as stretching and bending, to promote relaxation and healing. Swedish massage is known for its ability to help eliminate metabolic waste from the muscles, leading to improved blood circulation and reduced discomfort. (Sahraei et al. 2022). In a study conducted by Perlman et al. (2015), the researchers found that massage therapy had positive effects on patients with knee osteoarthritis. They specifically looked at massage techniques such as pe´trissage, effleurage, and tapotement, and discovered that these techniques led to significant improvements in pain, stiffness, functionality, and overall scores. Also, RA patients received a daily 30-min massage for eight weeks, resulting in noticeable relief from joint pain and improved neck mobility. This treatment proved to be effective in reducing joint pain caused by RA. Research has shown that massage therapy can effectively alleviate muscle spasms and pain, leading to a decrease in the reliance on pain medication among patients (Sahraei et al. 2022).

Balneotherapy

The term "balneotherapy" comes from the Latin word "balneum," which means "bath." It refers to the act of immersing oneself in thermal or mineral waters sourced from nature. In addition, it is worth noting that gases like CO2 or radon have the ability to enhance the properties of water which vary from country to country and are important variables in balneotherapy. It is the application of mineral water, peloids, or gasses to improve health, prevent disease, or treat a range of conditions promising as an adjunctive therapy and can help

RA patients improve their quality of life (Fernandez-Gonzalez et al. 2021). It has been used for a long time in classical medicine to treat a variety of conditions, and it is especially valued for its capacity to maintain or improve functional mobility, relieve pain, strengthen muscles, relieve spasms, and improve joint motion (Verhagen et al. 2004). In RA patients, it significantly improves physical performance and is a useful pain management technique because of its ability to ease muscular tension, lessen stiffness, and enhance overall comfort due to the warm, buoyant water (Bender et al. 2005). Although the specific mechanisms underlying balneotherapy remain unclear, potential contributors may include heat stimulation, the effect of the mineral salt content of baths, and the physical and chemical properties of mud packs (peloids) (Kocyigit et al. 2022; Fernandez-Gonzalez et al. 2021). In a recent study, Gonzalez et.al (2021) found compelling evidence supporting the beneficial impact of balneotherapy on the quality of life of patients with RA. Verhagen et.al. (2000) conducted randomized controlled trials on RA patients and found significant benefits. The results indicated short-term improvements in pain, stiffness, range of motion, daily living activities, and quality of life. The numerous advantages of balneotherapy encompass various aspects, including improvements in biomechanics such as joint unloading and enhanced muscle function, physiological changes like increased diuresis, and the potential for psychological benefits derived from the spa environment.

Acupuncture

It is a treatment modality used for over four thousand years in China and is considered an essential component of Traditional Chinese Medicine (TCM). It has been utilized to treat a variety of clinical disorders including conditions resembling RA. It includes the insertion of needles into specific body locations to relieve pain primarily through the modulation of neurotransmitters like endorphins or serotonin; its efficacy can be further enhanced with electrical current, known as electroacupuncture (Tam et al. 2007; Clement 2022; Chou & Chu 2018). In Israel, 41% of RA patients sought acupuncture treatment. A recent study conducted in Taiwan discovered that patients with RA frequently utilized TCM, such as acupuncture, with distinct usage patterns. In Korea, a significant majority (54.6%) of newly registered CAM users opted for acupuncture as their preferred choice (Clement 2022). Acupuncture either alone or in combination with other treatments showed beneficial effects on RA conditions without any reported adverse effects, and several possible mechanisms were identified including anti-inflammatory effects, antioxidative effects, and regulation of immune system function. These mechanisms contribute to the improvement in function and quality of life observed in RA patients undergoing acupuncture treatment (Chou and Chu 2018). In a study conducted by Tam et.al. (2007), it was found that acupuncture had a positive effect on reducing joint tenderness and improving the overall well-being of patients with RA. It was discovered that acupuncture had a significant impact on reducing systemic inflammation. This was evident through the decrease in levels of inflammatory indicators such as ESR and C-reactive protein (CRP), when compared to conventional care. Research has shown that there is potential for enhancing overall health and effectively managing symptoms (Berman et al. 2004).

Herbal treatments for RA

Before the late 1800s, folk remedies heavily relied on extracts from natural products. This shifted when biologically active organic compounds began to be isolated for medical purposes. In the past, herbal treatments were often used to treat rheumatological disorders, including RA. These treatments were favoured, because they contain bioactive compounds that have anti-inflammatory properties. These compounds can help regulate inflammatory pathways, decrease oxidative stress, and prevent the production of pro-inflammatory cytokines (Kaur A et al. 2012; Chaudhary and Fareed 2022). Plants such as *Cannabis, Withania somnifera, Terminalia bellerica, Emblica officinalis, Terminalia chebula, Boswellia serrata, Curcuma longa, Aconitum heterophyllym, Alpinia calcarata, Cissampelos pariera, Tinospora cordifolia (Guduchi), Cassia fistula (Amaltas), and Picrorhiza kurroa (Kutki)* have been used in formulations for arthritis (Singh et al. 2020). Ginger (*Zingiber officinale)* is considered one of the most useful herbal supplements that have been recommended to relieve symptoms of RA (Kaur A et al. 2012; Chaudhary and Fareed 2022). It has a variety of biological properties, particularly antioxidant and anti-inflammatory properties due to the presence of sesquiterpene Lactones (SLs) which are responsible for anti-inflammatory activity. Ginger extract is one of the effective arthritis joint pain remedies recommended by physicians (Kaur A et al. 2012). According to Aryaeian et al. (2019), daily consumption of ginger powder showed significant effects on the expression of immunity and inflammation intermediate factors, as well as reduced disease activity score in RA patients by modulating gene expression of inflammatory markers. Also, ginger supplementation significantly lowered the levels of important inflammatory biomarkers such as TNF-α, IL-1β, and IL-6, which are important in the development of RA (Askari et al. 2020). Ashwagandha *(Withania somnifera* Linn.) also known as Indian ginseng, is an important ancient plant and helps in providing progressive, long-lasting results for various health concerns like aging, anemia, arthritis, fatigue, sports fitness, and stress disorders (Kaur A et al. 2012; Chaudhary and Fareed 2022). Gupta et al. (2015) conducted an experiment on RA

patients and concluded that Ashwagandha powder followed by Sidh Makardhwaj with honey daily leads to significant improvement in tender joint counts, swollen joint counts, pain scores, and disability index due to anti-inflammatory, antioxidant and immunomodulatory properties of ashwagandha; it exhibits anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines and reducing inflammation in the joints. Cinnamon (*Cinnamomum cassia Presl*) is commonly used in traditional Oriental medicine. Cinnamaldehyde in C. cassia extract was found to have anti-inflammatory properties against RA. Cinnamaldehyde's therapeutic properties were demonstrated in vitro using activated macrophages (Raw246.7 cells) and in vivo with an adjuvant arthritis (AA) rat model. Cinnamaldehyde may reduce RA development by reducing IL-1β, regulating the succinate/HIF-1α axis, and blocking NLRP3. Cinnamaldehyde reduced synovial inflammation in AA rats and RA patients by reducing pro-inflammatory cytokine expression (IL-1β, TNF-α, and IL-6) (Zhao et al. 2021). Tripterygium wilfordii Hook F (TwHF) is a Chinese herb that possesses immunosuppressive properties and has traditionally been used to treat RA. Numerous preclinical investigations have indicated that TwHF root extracts decrease the expression of pro-inflammatory cytokines and mediators, adhesion molecules, and matrix metalloproteinases in macrophages, lymphocytes, synovial fibroblasts, and chondrocytes. TwHF can also cause apoptosis and limit proliferation in lymphocytes and synovial fibroblasts. TwHF extracts have been shown to have immunosuppressive, cartilage-protecting, and anti-inflammatory properties, making them a viable treatment option for people with RA who have failed conventional therapies (Lindler et al. 2020).

Conclusion

In conclusion, RA is an autoimmune disease characterized by joint deterioration, inflammation, presence of ACPAs and RF. Hormones such as estrogen, progesterone, and testosterone have been shown to impact immune function and have anti-inflammatory properties, suggesting their involvement in the development and management of RA. HRT and SERM have demonstrated potential benefits in managing RA in postmenopausal women. Additionally, complementary therapies such as herbal treatments, Swedish massage, and balneotherapy have shown promising effect in managing RA symptoms. Further investigation is needed to understand the roles of hormones and complementary therapies in regulating immunological responses and inflammation in RA. Additionally, exploring novel therapeutic targets like cytokines could lead to more personalized and effective treatments for RA.

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Declarations

Conflict of interest The authors have not disclosed any competing interests.

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