



# The Impact of Menopause on Autoimmune and Rheumatic Diseases

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## Abstract

The prevalence of autoimmune and rheumatological diseases is significantly higher in women, likely due to the effect of sex hormones influencing the development and function of the immune system, a phenomenon observed particularly during pregnancy. Oestrogens, in particular, appear to be a major factor in modulating the immune response, as their receptors are present in nearly all immune cells, where they regulate the expression of genes involved in inflammation. However, there is limited data on how menopause impacts autoimmune diseases, despite evidence suggesting that the menopausal perturbation of hormone levels may lead to the development of autoimmune conditions or alter the course of an already established disease. This review focuses on rheumatic conditions, aiming to provide a comprehensive understanding of how menopause influences the onset, progression, and clinical features of autoimmune diseases. The best evidence is available for rheumatoid arthritis and systemic lupus erythematosus, two paradigmatic autoimmune diseases in which menopause elicits opposite outcomes. Despite these data, there is a notable lack of evidence and research on the impact of menopause in other inflammatory arthritis and connective tissue diseases. This gap highlights a crucial area for future research and unmet needs to be addressed. Understanding how menopausal changes impact autoimmunity and rheumatic diseases will be crucial for improving the management of autoimmune and rheumatological diseases in women.

**Keywords** Rheumatic diseases · Menopause · Autoimmunity onset · Oestrogens

## Introduction

Menopause is defined as the permanent cessation of menstrual periods for at least 12 months, determined retrospectively, without an underlying pathological cause. It usually occurs on average between 45 and 55 years of age, reflecting ovarian follicular depletion, leading to hypooestrogenism and elevated follicle-stimulating hormone (FSH) levels [1].

The onset of menopause can influence the course of rheumatic diseases and notably some systemic symptoms are shared between menopause and immune-rheumatic conditions. These include psychosocial factors, sexual

dysfunction, dyspareunia, vaginal dryness and an overall lower quality of life [2–6]. Joint pain and stiffness are more common in post-menopausal women compared to their pre-menopausal counterpart, regardless of age. In fact, menopause is also associated with diffuse musculoskeletal pain [7]. It has been proved that changes or loss (natural, autoimmune, pharmacological, or surgical) of sex hormones directly influences musculoskeletal pain susceptibility, which is partially improved and alleviated by hormone replacement therapy [8]. Loss of oestrogens may also contribute to ‘inflammaging’, the pro-inflammatory state associated with aging, which plays a role in the development of degenerative conditions such as osteoarthritis [9]. Furthermore, sex hormones influence the development and function of the immune system and also contribute to gender differences in disease risk [10]. Women are overall more affected by autoimmune diseases than men, with particularly high female-to-male ratios for connective tissue diseases: 9:1 for systemic lupus erythematosus (SLE) and Sjogren’s syndrome [10], 3:1 for systemic sclerosis [11]. The various forms of arthritis present variable sex ratios: rheumatoid arthritis (RA) is three to four times more common in

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women [10, 12], while ankylosing spondylitis has a slight male predominance [10]. Epidemiology data suggest that although the prevalence of autoimmune diseases is higher in women, the incidence and course of different rheumatic diseases varies across reproductive stages, reflecting hormone fluctuation. Menopause seems to be a turning point in the interaction between age and immune function [13]. Age-related changes in the female immune response, driven in part by the decline in oestrogen levels, may impact course and progression of these sex-related diseases.

## The Immunology of Menopause Timing

A relevant immunological paradigm related to menopause comes from the study of immune cell dysfunctions in premature ovarian insufficiency (POI) [14], a condition where menopause occurs before the age of 40, with a worldwide prevalence of 3.7% [15, 16].

Several physiological pathways are involved in the pathogenesis of POI. Several cases remain idiopathic, but growing evidence points to a strong genetic component. The age at menopause follows family inheritance, and X chromosome defects are the main genetic contributors. Mutations in somatic genes appear to be also involved, as genes involved in meiosis progression and in folliculogenesis. Nevertheless, the X chromosome seems to play the major role, with aneuploidies, mosaicism, partial loss of the long arm of the X, translocations, polymorphisms, and mutations in several genes being associated with both pleiotropic syndromes, as Turner or Fragile X syndrome, or isolated cases of POI [16]. Evidence suggests that POI has a peculiar pathogenesis, involving also immunologic factors, with immune cells alterations that cannot be extended to all menopausal women, considering the variable immune assets. The immunological differences between POI and average menopause are discussed below and illustrated in Table 1. Specifically, classical monocytes seem decreased and exhibit an impaired function and an exhausted phenotype; natural killer (NK) cells also appear to be reduced and show altered expression in genes involved in the IL-17 signaling, cellular adhesion, and cytotoxicity pathways. In contrast, B cells and plasma

cells appear to be increased in number compared to healthy controls, with upregulation of genes involved in T cell receptor signaling pathways and enhanced autoantibody production. In addition, T-regulatory (Treg) cells are reduced in POI, with an increased CD4/CD8 ratio compared with healthy controls. These alterations suggest a dysregulated immune response, which may itself contribute to the development of POI [14]. Autoantibodies have been described in patients with POI, with prevalence rates ranging from 24 to 73%. These autoantibodies target several antigen involved in the reproductive systems, including proteins derived from oocytes, zona pellucida (the extracellular material surrounding the oocyte), protein involved in the process of fertilization, as heat shock proteins, alpha-actinin 4, and beta-actin, or metabolic enzymes as enolase, involved in the glycolytic pathway [17, 18]. Lymphocytic oophoritis, characterized by T cell and plasma cell infiltration, has been described in ovarian samples from patients with POI, as further data supporting the role of immune dysfunction in the development of early menopause [19].

A systemic immune dysfunction may also account for the strong association of POI with a range of autoimmune conditions, most commonly thyroiditis (27%), followed by diabetes mellitus (2.5%), and other disorders such as Addison's disease, autoimmune polyglandular syndromes, hypophysitis, thrombocytopenia purpura, vitiligo, autoimmune hemolytic anemia, RA, SLE, primary biliary cirrhosis, and hepatitis [17, 20]. Studies have shown a high prevalence (40%) of at least one autoimmune condition, among Hashimoto's disease, SLE, RA, psoriasis, Crohn's disease, polyglandular autoimmune syndrome and coeliac disease, in women with POI. This suggests that these women, presenting with POI, might deserve a screening for an underlying autoimmune disease; a rheumatologic evaluation can be advocated in all women with POI [21]. This paradigm suggests the close interrelationship between menopause and autoimmunity, where one can trigger or exacerbate the other. On the other hand, the impact of late menopause, i.e., menopause after 55 of age, associated with prolonged oestrogen exposure, has yet to be clarified. It remains to be investigated whether this might be a protective or risk factor for autoimmune conditions and related symptoms.

**Table 1** Immune alterations described in premature ovarian insufficiency (POI) and in average menopause

	Premature ovarian insufficiency	Average menopause
Monocytes	Reduced number; exhausted phenotype	M1 pro-inflammatory polarization, production of cytokines such as IL-1, IL-6, IL-17A and TNF-alpha
B cells	Increased number; enhanced autoantibody production	Decreased B lymphocytes and antibody release
T cells	Increased CD4/CD8 ratio; reduced Treg number	Th1 response, reduced Treg with higher ratio of Th17 cells to CD4 + CD25 + Foxp3 + regulatory T cells, decreased CD4
NK cells	Reduced number; altered gene expression with pro-inflammatory signature	Increased cytotoxic activity

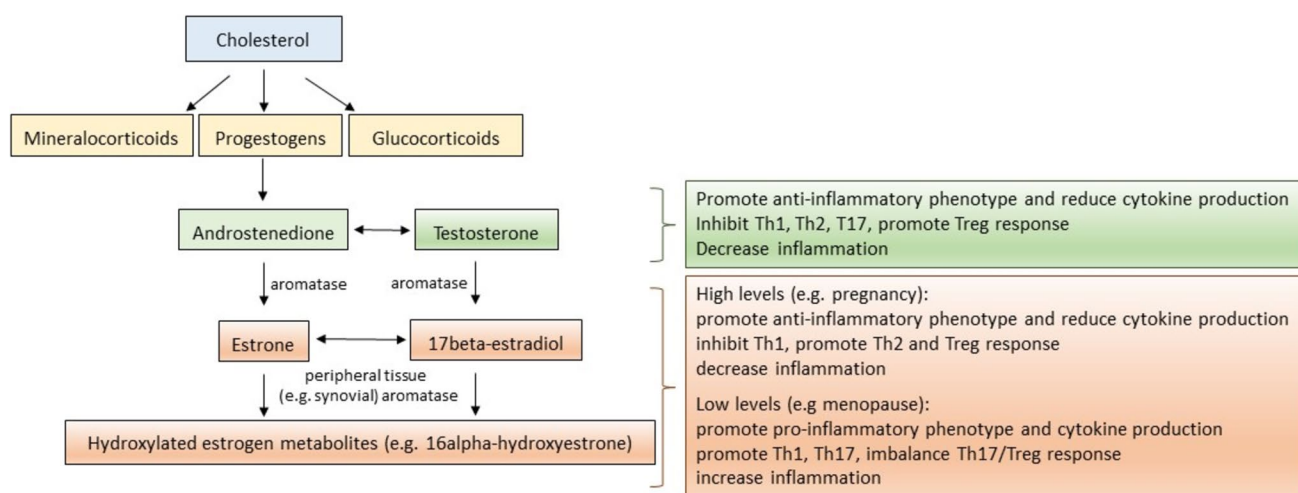
Women diagnosed with rheumatic diseases frequently experience changes in disease activity after menopause, potentially due to changes in gonadal hormone levels or the ratio of androgen to oestrogen [22]. This review will describe the changes that occur at menopause from the perspective of autoimmunity and chronic inflammatory rheumatic diseases.

## Hormone Modifications and Development of Autoimmunity in Menopause

Sex hormones include androgens, oestrogens and progestogens, which control reproduction and influence various systems, including the immune response [23]. They are mainly produced by the gonads and have cholesterol as a precursor, which is also common to other hormones such as glucocorticoids, mineralocorticoids and vitamin D (Fig. 1) [24]. Among these, oestrogens are the most studied and their impact on immune response, inflammation, and autoimmunity is well described.

Estrone and 17beta-estradiol are the first oestrogens produced through the steroid hormone pathway; while estrone is a weak hormone, produced by the ovaries, adrenal glands, and peripheral tissues, especially adipose tissue, 17beta-estradiol is the most potent form of oestrogen, synthesized predominantly in the ovaries from testosterone via the enzyme aromatase. Both estrone and 17beta-estradiol can be further metabolized into downstream hydroxylated oestrogen metabolites, which can modulate immune cell response and induce cytokine production [25] (Fig. 1). Oestrogens bind to three functionally distinct receptors (ER alpha, beta, and the G-protein coupled receptor), present in nearly all immune cells, including T cells, B cells, dendritic

cells, neutrophils, macrophages, NK cells, thymus stromal cells, and bone marrow cells. Upon binding to oestrogen, these receptors translocate to the nucleus, where they regulate the expression of target genes, among which are genes regulating inflammation. Furthermore, oestrogens mediate also non-genomic signaling pathways. Notably, the effect of oestrogens on target cells is biphasic, with enhancement of inflammation at cyclical/low doses and inhibition at chronic/high concentrations, as seen during pregnancy [22]. The molecular mechanism of oestrogen function is complex and is primarily mediated by two nuclear receptors, ER $\alpha$  and ER $\beta$ , which are encoded by different genes and have overlapping, opposing, or independent functions depending on the cell type. ER $\alpha$  is the most widely expressed, especially in immune cells, and some variants are also found on the plasma membrane and promote rapid nongenomic signaling. In the absence of oestrogen, ERs are inactive in the cytoplasm or nucleus, bound to heat-shock protein complexes. Upon oestrogen binding, the receptor undergoes a conformational change, leading to its activation. It then dimerizes, translocates to the nucleus, and interacts with oestrogen response elements or other transcription factors to regulate gene transcription. The recruitment of coregulators to these complexes plays a key role in determining the transcriptional response. Further complexity is related to other signaling pathways, like those involving MAPK, which can influence the activation of ERs even without a classical ligand. Oestrogens exert their effects mainly through ER alpha, predominantly present in reproductive tissues, as uterus and ovaries, but also in bone, liver, brain, and immune cells, thus modulating reproductive, metabolic, and immune functions [26, 27]. Oestrogens can regulate macrophage function, both inflammatory and non-inflammatory cytokine production, T cell differentiation towards Th1, Th2, or Treg cells, and



**Fig. 1** Sex hormone metabolism and impact on inflammation

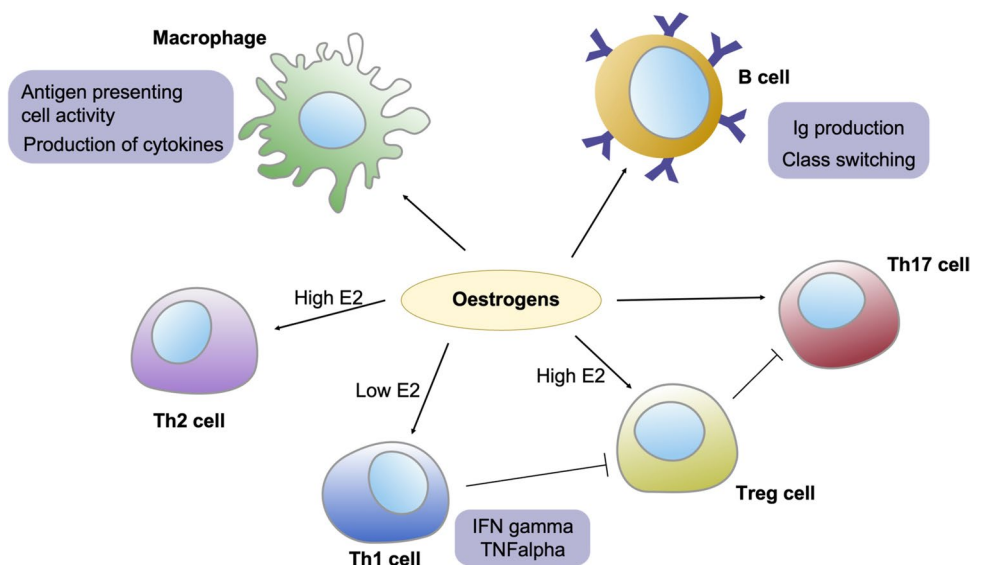
B cell function, influencing antibody production (Fig. 2). Oestrogens, particularly estradiol (E2), play a significant role in regulating macrophage biology. They influence macrophage differentiation by regulating macrophage colony-stimulating factor (M-CSF). In certain settings, oestrogens also regulate the recruitment of monocytes and macrophages to sites of inflammation, infection, or tumors [27]. Oestrogens also influence cytokine production by macrophages, with both positive and negative effects, depending on factors like the oestrogen type, exposure duration, macrophage origin, and oestrogen levels. The ER $\alpha$ /E2 complex can also increase the expression of suppressor of cytokine signaling 3 (SOCS3), which modulates the JAK/STAT pathway, affecting both pro-inflammatory and anti-inflammatory cytokines. E2 also plays a significant role in macrophage polarization, mainly towards an M2-like phenotype, promoting resolution of inflammation and tissue repair, although it can also influence M1 polarization in some cases, particularly by enhancing STAT1 activity, which promotes pro-inflammatory responses [27, 28]. This dual effect of E2 on macrophage polarization highlights its complexity and suggests that oestrogen signaling may induce different immune effects depending on the context.

Adaptive immunity can also be affected by oestrogens. Thymic T cells progenitor proliferation is reduced by elevated oestrogen levels [29]. Furthermore, high oestrogen levels, as in pregnancy, affect differentiation of T cells into CD8 and CD4, promote a Th2 response, and increase Treg proportion. TNF $\alpha$  and IFN $\gamma$  are inversely regulated by oestrogen levels [27]. Oestrogens have a significant impact on B cell development and antibody production. E2 impairs B cell differentiation and promotes the survival of autoreactive B-cells, by the expression of anti-apoptotic proteins, which may contribute to the higher incidence of

autoimmune diseases in females. Oestrogens regulate class switch recombination in B cells, promoting the transition from IgM to IgG production, which can increase the antibody repertoire. However, this process also raises the likelihood of mutations associated with autoimmune diseases and B cell malignancies [30, 31].

Of note, oestrogen play a key role in bone metabolism by affecting osteoblasts, osteoclasts, and osteocytes. Osteogenesis and mesenchymal stem cells differentiation into osteoblasts is increased by oestrogen-activated pathway of WNT/ $\beta$ -catenin and BMP. Osteoblasts are also induced to produce growth factors like IGF1 and TGF $\beta$ , enhancing bone formation. On the other hand, osteoclast formation and activity is suppressed, by the increased expression of osteoprotegerin, which inhibits RANKL, reducing bone resorption. Osteoclast apoptosis is also induced via TGF $\beta$  production, whereas oestrogen deficiency leads to increased RANKL expression and osteoclastogenesis [32]. Furthermore, in peripheral tissues, the conversion of oestrogens into hydroxylated metabolites can modulate the function of immune cells; in RA, the synovial aromatase activity is increased by locally produced inflammatory cytokines, leading to intracrine synthesis of active oestrogen metabolites within the tissue target of the immune response, thus modulating the activity of monocytes/macrophages. A similar mechanism also occurs in normal tissues during aging [25]. Therefore, different sex hormone levels, as occurs at specific time points of the female reproductive life, modulate the immune response, as observed in patients with autoimmune and rheumatic diseases, where variations in the risk of onset or flare of disease based on hormonal changes, as occurs at menarche, pregnancy, or menopause, are evident in some diseases more than others, accounting for different underlying autoimmune mechanisms. The different behavior of

**Fig. 2** Schematic representation of the impact of oestrogens on immune cells



specific diseases at different times in reproductive women's lives is summarized in Table 2 for puberty and pregnancy, in Table 3 for menopause, with detailed the impact on the onset and on the course of the disease.

During menopause, the expression of ERs may vary and is well described in some tissue, as in the brain, but less studied in immune cells. It seems that monocytes in premenopausal women have lower ER RNA levels compared to males and postmenopausal women, B and T lymphocytes do not show differences in ER RNA levels in different menopausal age [26]. Therefore, the different oestrogen levels and the variations in their receptors on target cell in menopause can account for the altered immune response in postmenopausal women.

Therefore, menopause represents the critical intersection between the effects of aging and hormonal changes, with significant consequences on the immune response, as summarized in Table 1. With menopause, the decline in

oestrogen levels, accompanied by the rise in gonadotropins, and the overall impact of aging all contribute to immune modifications. The role of oestrogen loss in the development of inflammation can be inferred from studies showing that women with sudden oestrogen deficiency following surgical oophorectomy exhibit high levels of inflammatory cytokines and a polarization towards pro-inflammatory immune cells [33], a phenomenon similar to that described in the elderly population [9]. With aging, immunosenescence occurs and immune cells acquire a pro-inflammatory phenotype [34], with epigenetic modifications implicated as one of the main pathogenetic mechanisms of autoimmunity. In fact, epigenetic modification have been described in autoimmune diseases as SLE [35] and RA [36], and the decline in oestrogen levels has been proposed to further enhance epigenetic changes promoting immune polarization. This can be the link between genetics, hormones, and environment and can play a pivotal role in the pathogenesis and in the

**Table 2** Impact of hormonal changes on autoimmune and rheumatic diseases at specific times in reproductive women's lives, such as puberty and pregnancy

	Puberty	Pregnancy	Ref
Rheumatoid arthritis	Early age at menarche increases risk	Improved disease activity	[65, 119, 120]
Psoriatic arthritis	Longer fertile timeframe associated with reduced risk of disease	Slight improvement in disease activity	[56, 121, 122]
Systemic lupus erythematosus	Increase incidence in girls after puberty Increase prevalence and titers of ANA Mean menarche age higher in patients with juvenile SLE	Flares more common	[4, 59, 123–126]
Sjogren syndrome	Reduced lifetime exposure to sex hormones associated with increased risk of the diseases	Disease might worsen and be complicated by pulmonary hypertension	[127, 128]
Systemic sclerosis	Late age at menarche associated with reduced risk of the disease	Disease generally stable, but pulmonary hypertension may dramatically worsen	[129–131]
Autoinflammatory diseases (Familiar Mediterranean Fever)	Uncontrolled disease may affect the onset of puberty	No definite improvement or worsening of disease attacks	[90, 132]

**Table 3** Risk of rheumatic disease onset and modification of disease course in menopause

	Menopause		Ref
	Disease onset	Disease course	
Rheumatoid arthritis	3:1 risk females to males	Worse disease outcomes, disability, and quality of life	[65–67]
Psoriatic arthritis	1:1 risk females to males	NA	[133]
Systemic lupus erythematosus	5:1 risk females to males	Improved disease activity, decreased frequency and magnitude of flares	[59, 76–78]
Sjogren syndrome	9:1 risk females to males	NA	[134]
Systemic sclerosis	NA	Improved skin fibrosis, increased risk of developing pulmonary hypertension in patients with limited form of the disease	[85, 86]
Autoinflammatory diseases (Familiar Mediterranean Fever)	Not applicable	Improvement in ~50% cases	[91]

NA, non-available data

modifications of the clinical manifestations of autoimmune diseases [5, 37].

In postmenopausal women, immunosenescence can be exacerbated by the loss of oestrogens, which leads to further elevation of cytokines such as IL-1, IL-6, IL-17A and TNF- $\alpha$  [13, 38–44]. Importantly, all these cytokines are relevantly associated with the pathogenesis of inflammatory arthritis and represent targets of the available biotechnological drugs. Notably, surgical menopause also leads to similar increase in these cytokines [45], further supporting the important role of loss of oestrogens in driving inflammation. Additionally, in postmenopausal women, peripheral blood leukocyte composition undergoes changes, including a reduction in neutrophil percentage and an increase in lymphocyte percentage, resulting in lower neutrophil-to-lymphocyte ratio [46]. Other changes from reproductive to postmenopausal age encompass Th1 polarization of lymphocytes, increased cytotoxic activity of NK cells, higher ratio of Th17 cells to CD4 + CD25 + Foxp3 + regulatory T cells [13], and decreased CD4 T and B lymphocytes [47]. During menopause, there is an overall decrease in B cell activity and antibody release [24], opposed to what occurs to women with POI or with unexplained infertility [14, 18].

### Impact of Menopause on the Onset of Rheumatological Diseases

The menopause may trigger the development of autoimmune rheumatic diseases; the most studied and described is RA, which is often diagnosed within a few years before or after menopause [48] and where the female predominance is reversed beyond the age of 75 [12] (Table 3).

The relationship between hormonal fluctuations, particularly the drop in oestrogen, and the development of autoimmunity in RA has been investigated. As women transition into menopause, the decrease in oestrogen levels may directly impact the complex interplay between genetic predisposition and immune regulation. Genetic susceptibility for RA is mainly due to the presence of HLA-DRB1, the so-called ‘shared epitope’. In addition, other genes involved in immune signaling, such as those encoding peptidyl arginine deiminase type 4 (PAD4), a calcium-dependent enzyme catalyzing the conversion of arginine residues to citrulline, protein tyrosine phosphatase 22 (PTPN22), which tunes T and B cell antigen receptor signaling, and several pro-inflammatory cytokines, are crucial for the development of RA. As previously reported, under normal conditions, oestrogens play an immunomodulatory role, regulating immune cell activity. In postmenopausal women, the loss of oestrogens may alter this balance, leading to an uncontrolled amplification of the effects of these genes. Genetically predisposed women, under conditions of oestrogen deficiency,

i.e., in postmenopausal state, may develop specific CD4 + T lymphocytes subsets with auto-reactive properties, as Th17 cells, with Th17/Treg imbalance, leading to release of inflammatory cytokines and stimulation of autoreactive B cells that promote RA pathogenesis and perpetuate the inflammation [49]. Furthermore, one distinctive feature of RA in the presence of anti-citrullinated protein antibodies (ACPA); citrullinated neoantigens are formed with a process where the amino acid arginine is converted into citrulline, creating potentially new, immunogenic epitopes. They can stimulate the dysregulated immune system of menopausal women, leading to the production of ACPA [49]. It has to be noted that PAD isoenzymes, present in a variety of female tissues, including ovaries, breasts, and cells of the anterior pituitary gland, are sensible to oestrogens, as they regulate PAD expression in these tissues, leading to fluctuating PAD levels throughout the female reproductive cycle. As PAD expression is stimulated by oestrogen (specifically E2) and suppressed by androgens, it can be expected that higher levels of oestrogen could result in increased citrullination of proteins. This, in turn, could lead to a higher exposure to autoantigens, potentially contributing to the development of autoimmune responses associated with RA [50]. This may potentially conflict with data showing the onset or worsening of RA during menopause. However, given the complex interplay between immune cells and hormones, these findings are not mutually exclusive. In fact, they highlight the significant impact of declining oestrogen levels (i.e., menopause) on the immune system and its alterations. This decline likely contributes to, or possibly even triggers, disease progression in patients who may have already had considerable exposure to autoantigens.

In addition, oestrogens influence the glycosylation of autoantibodies, regulating the glycan composition of the fragment crystallizable region (Fc) region of autoantibodies. In fact, oestrogens induce the expression of the sialylation enzyme  $\beta$ -galactoside  $\alpha$ 2,6-sialyltransferase 1 (ST6Gal1) in plasmablasts. In menopause, the lower sialic acid residues on Fc glycans of RA autoantibodies increases their pro-inflammatory activity, thus further contributing to RA pathogenesis [51]. It has been demonstrated that in first-degree relatives of patients with RA, serum ACPA positivity and therefore an increased risk of developing RA, is associated with menopause [52]. In addition to the systemic effects, oestrogens may also play a significant role in local inflammation within tissues. The peripheral conversion of androgens to oestrogens, proved increased in the inflamed synovial tissue, leading to local production of hydroxylated oestrogen metabolites, thus enhancing inflammation and autoimmunity [25]. High oestrogen concentrations have

been found in the synovial fluids of patients with RA of both sexes, mainly due to hydroxylated forms, in particular 16 $\alpha$ -hydroxyestrone, with effects on synovial cells such as macrophages and fibroblasts, inducing their proliferation thus promoting the formation of the ‘pannus’, typical of RA [53]. A later menopause has been associated with a lower risk of developing RA, further suggesting a protective role of oestrogens for the onset of disease [54]. It has been suggested that the early menopause may induce RA onset and worsen RA symptoms, possibly due to the loss of the oestrogen immunomodulatory effects. Age at menopause should be considered when assessing RA, with early menopause potentially having more severe clinical implications [55].

Although data from other inflammatory arthritis are limited, a longer reproductive period has also been associated with a reduced risk of skin psoriasis and psoriatic arthritis (PsA). A prospective study showed that postmenopausal women without underlying psoriatic diseases had a reduced risk of developing psoriasis and PsA if age at menopause was greater than 55 years [56].

Menopause can also influence the risk of connective tissue diseases. Pre-menopausal women have a significantly higher risk of developing SLE compared to their post-menopausal counterparts. Late-onset SLE, which occurs after the age of 50, when oestrogen levels are more similar between genders, shows a female-to-male incidence ratio of about 5:1, significantly lower compared with younger ages, when it reaches ratios of 9:1–15:1, particularly in non-Caucasian women [12] (Table 3). Women who develop SLE after menopause have distinctive clinical features, as less frequent malar rash, renal disease, leukopenia, positive ANA, anti-double-stranded DNA antibodies and hypocomplementemia than women with onset in fertile age, ultimately representing a less severe disease with a more favorable natural history [57]. Furthermore, early age at menarche, use of oral contraceptive, early age at menopause, surgical menopause, and postmenopausal use of hormones appear to be associated with an increased risk of SLE [58, 59], thus confirming the relevant role of sex hormones in modulating the disease.

Sjogren’s syndrome exhibits a peculiar hormonal profile, which may explain its clinical manifestations, particularly its peak incidence in menopausal age. Oestrogens seem to protect acinar cells of exocrine glands from atrophy and apoptosis [60]. The menopause-associated decrease in oestrogen levels may induce an increase of apoptosis of secretory gland acinar cells. While male gonads produce testosterone with exocrine production of dihydrotestosterone (DHT), which has anti-apoptotic properties, oestrogen-deficient women produce dehydroepiandrosterone-sulfate (DHEAS) in the adrenal glands and then convert it to DHT in the exocrine glands. Low levels of DHT appear to be associated with development of Sjogren’s syndrome, both in men and women. Apoptosis of acinar cells is increased

in a low-oestrogen context, as is pro-inflammatory polarization of immune cells. Both these pathways may concur to the pathogenesis of Sjogren’s syndrome in post-menopausal women, when altered presentation of exocrine gland self-antigens by antigen presenting cells may activate T and B cells, leading to autoimmunity against exocrine glands [61]. In murine models, decreased oestrogen levels lead to infiltration of lymphocytes in lacrimal gland, apoptosis, production of autoantibodies such as Ro/SSA, La/SSB, anti- $\alpha$ -fodrin, and Sjogren syndrome-like symptoms [62].

## Impact of Menopause on the Course of Rheumatological Diseases and Role of Hormone Replacement Therapy

Considering the high impact of hormonal fluctuations on the immune system, it is intuitive that established autoimmune-rheumatic diseases may undergo modifications in clinical course according to hormonal status. A description of the modifications in the course of immune-rheumatic diseases occurring in menopause is summarized in Table 3.

It should be noted that menopause may also worsen complications of rheumatic diseases, in parallel with the changes of immune response. This is the case with osteoporosis, which becomes prevalent after menopause, with an increased risk of bone fragility fractures, particularly in patients affected by rheumatic diseases. Early menopause and the cumulative dose of glucocorticoids have the main impact on this complication. Early atherosclerosis is another burden of rheumatic diseases, particularly RA and SLE, and can be influenced and accelerated by menopause [4].

## Inflammatory Arthritis

The age of menopause has been associated with different clinical phenotypes of arthritis, well represented by the fact that early menopause is associated with seropositive RA [63], higher disease activity and worse patient-reported outcomes in global assessment, fatigue, sleep disturbance, and quality of life, even after adjustment for age, disease duration, and treatment [64]. In women with established RA, menopause negatively affects the course of the disease. It is associated with worse outcomes, disability, and quality of life. Menopause negatively affects the functional decline [65], in contrast to ever having used hormone replacement therapy, having had a pregnancy, and having had a longer length of reproductive life, which are all associated with reduced functional decline. Disability is worse in post-menopausal than in pre-menopausal women with RA, regardless of age, disease duration, or radiographic damage [66]. Joint damage and disability are greater in postmenopausal female patients and the menopausal state appears to be the main

factor explaining the differences in outcome between men and women in RA [67].

Although the role of oestrogens appears beneficial, studies on their exogenous use in RA yield conflicting results [55]. Overall, oral contraceptives, in particular the newer formulations with a lower oestrogen and higher progestin content, appear to have a small protective effect [68]; in menopausal women, hormone replacement therapy reduces the risk of ACPA-positive RA, whereas it does not affect the development of ACPA-negative RA. In established RA, the use of hormone replacement therapy does not appear to be associated with disease flares [69, 70].

The impact of menopause in spondyloarthritis is less well-established than in RA; one study reported an inverse correlation between erythrocyte sedimentation rate and oestrogen levels in patients with ankylosing spondylitis, with an improvement of peripheral arthritis and clinical activity with oestrogen replacement therapy [71]. On the other hand, oestrogens seem not to influence radiographic progression [72]. Conclusive studies in PsA are lacking, and data are conflicting for skin psoriasis, with some studies showing no impact of menopause [73], other reporting exacerbations of disease [74]. The role of hormone replacement therapy has not been elucidated.

### Systemic Lupus Erythematosus and other Connective Tissue Diseases

Women with SLE experience menopause at a median age of 50 years, which aligns with the general population. However, early menopause is often associated with early SLE onset, younger age at the initiation of cytotoxic treatments such as cyclophosphamide, induction of remission using cyclophosphamide, higher disease activity, and Hispanic origin [75]. As expected, prolonged treatment with cyclophosphamide, particularly when started at an older age (over 32 years), increase the risk of gonadal failure [4]. Women entering menopause tend to show an improvement in disease course, in terms of SLE Disease Activity Index (SLEDAI) and decreased frequency and magnitude of flares. However, a greater accumulation of damage in the target organs has been described after each flare [59, 76–78]. The use of hormone replacement therapy in women with SLE has been linked to an increased risk of mild to moderate flares [79]. Oestrogens stimulate the production of polyclonal immunoglobulin G (IgG) by peripheral blood mononuclear cells derived from SLE patients, but not from healthy donors, with increased release of autoantibodies including anti-double-stranded DNA, whose titre increases during disease flares [80]. Studies from the LUMINA (LUpus in MInorities, NAture versus nurture), a multiethnic, longitudinal cohort, has highlighted

peculiar findings regarding the impact of menopause on SLE. It was described that renal involvement is more common in premenopausal women, while arterial vascular events are more frequent in postmenopausal women. All other disease manifestations and global disease activity remain similar, regardless of menopausal status. However, organ damage appears to accumulate more rapidly in menopause. After adjusting for confounders, it was described that age, rather than menopause itself, is independently associated with damage accrual, renal involvement, and vascular arterial events in SLE women [59]. This is further supported by another study reporting a constant improvement in disease activity over time in SLE patients, independently of menopause, suggesting that menopause may not be the primary factor influencing the disease course [78]. As in the general population, the use of exogenous oestrogens increases the risk of thrombosis in women with antiphospholipid antibodies and should be avoided in seropositive SLE women [81].

In the case of Sjogren's syndrome, the onset of the disease often coincides with the perimenopausal period, and its symptoms, such as vaginal dryness and dyspareunia, are frequently mistaken for those related to menopause. The specific impact of menopause on Sjogren's syndrome has not been widely studied [4]. Trials evaluating the role of DHEAS have failed to demonstrate benefits on the clinical manifestations of the disease, even in patients with low serum DHEAS levels. This may be attributable to inability of exocrine gland tissue to convert DHEAS into its active form [82]. In contrast, a case-control study has described that the use of hormone replacement therapy, whether oestrogen-only and combined, may act as a risk factor for the development of Sjogren's syndrome [83].

For patients with systemic sclerosis, menopause often occurs earlier in life. Young age at disease onset and presence of digital ulcers are significantly associated with younger menopausal age [84]. Menopause appears to directly influence skin fibrosis and arterial complications in systemic sclerosis. Postmenopausal women exhibit less skin fibrosis, as determined by modified Rodnan skin score, with lower scores compared to their fertile counterparts, regardless of age or disease duration. This may be attributed to the role of oestrogens in stimulating skin fibroblasts to produce extracellular matrix proteins, and monocytes/macrophages in release transforming growth factor-beta 1 (TGF-beta 1) and platelet-derived growth factor (PDGF), thus promoting skin fibrosis. The impact of menopause on skin thickening is more evident in women with the diffuse form of the disease [85]. On the other hand, women with the limited form of systemic sclerosis, usually associated with anti-centromere antibodies, may have an increased risk of developing pulmonary hypertension after menopause [86].

Hormone replacement therapy might play a role in preventing this severe complication [87].

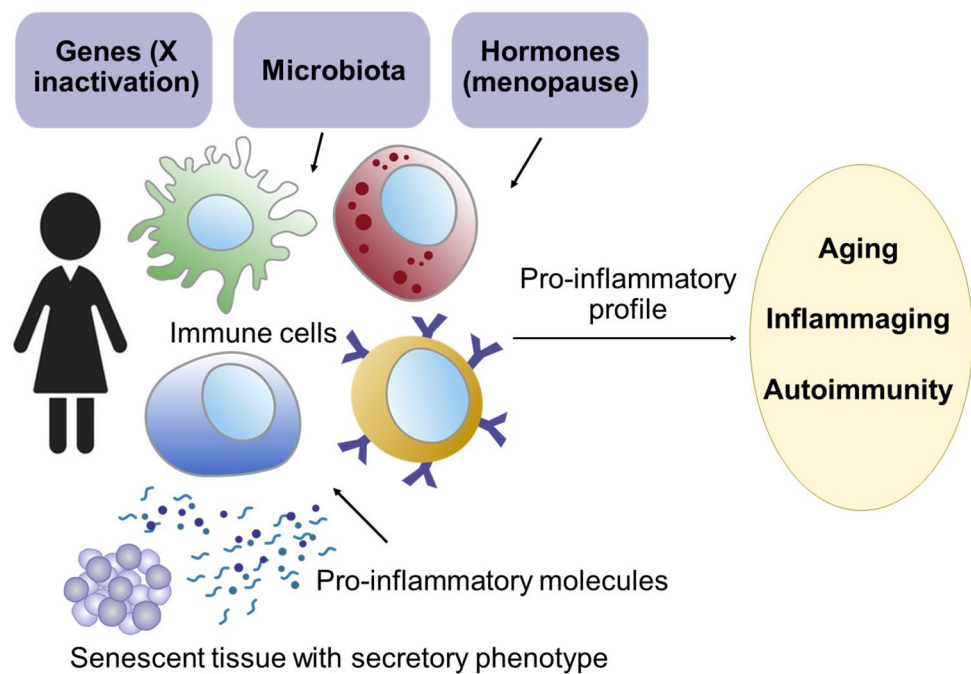
Despite these data, a systematic literature review pointed out the limited number of studies on hormone replacement therapy in systemic sclerosis, concluding that there is a lack of recent high-quality trials [88]. This highlights the importance of a better understanding of the immune mechanisms triggered by menopause, to improve management of rheumatic diseases.

A discussion is warranted also for autoinflammatory diseases in which flares / attacks can be triggered by the menstrual cycle, as described particularly in women with Mediterranean Familial Fever [89]. Thus, a fluctuation in sex hormone levels may trigger flares of the disease while during pregnancy, a definite trend towards improvement or worsening has not been described [90]. The impact of menopause is also unclear. In one study, around 50% of patients reported a reduction in the frequency and intensity of attacks [91]. In another specific setting, osteoporosis is characterized by decreased bone density and increased fracture risk, which can be exacerbated by the hormonal changes, in particular oestrogen loss, that occur after menopause [92]. In autoimmune and rheumatic diseases, it is a significant concern in women. When coupled with the inflammation and immune dysregulation associated with many rheumatic diseases, in particular with elevated disease activity, osteoporosis may be more pronounced and can occur earlier than in the general population [93]. In fact, inflammatory cytokines as TNF- $\alpha$ , IL-6, and IL-1 play a direct role in bone resorption, increasing the activity of osteoclasts and interfering with the balance between osteoblasts and osteoclasts, leading to a higher rate of bone loss [94]. In female patients with RA, the risk of postmenopausal osteoporosis is twice as high compared to age-matched women without RA. This can be due to immune dysregulation caused by oestrogen deficiency, which increases the ratio of Th17 cells to Treg cells and boosts IL-17 production. IL-17 promotes inflammation and bone resorption, leading to chronic inflammation and exacerbated bone destruction. Additionally, B-cells, activated by Th17 cells, produce ACPA, that independently contribute to bone resorption [95]. The presence of ACPA alone has been shown to be associated with reduced bone mineral density, independent of disease activity or other confounding factors [96]. The prolonged use of glucocorticoids, also at low doses, for treatment of autoimmune and rheumatic disease is another relevant risk factor for severe postmenopausal osteoporosis, as they inhibit bone formation, increase bone resorption, and reduce calcium absorption [4]. The reduced physical activity associated with rheumatic diseases, especially those with joint pain and damage as in RA, can further contribute to bone loss [93].

## Confounding and Possibly Unsuspected Sex-Related Factors

There are less obvious pathways that may play a role in the modification occurring during menopause, particularly related to autoimmunity, and might deserve investigation. One relevant factor is the cervico-vaginal microbiota, which undergoes changes with menopause [97]. This may contribute to the onset of vaginal symptoms as dyspareunia and vaginal dryness. Furthermore, the cervico-vaginal mucosa is crucial for maintaining homeostasis with the vaginal microbiota, predominantly composed of *Lactobacillus*, while operating immunological surveillance protecting against pathogenic organisms. In the human ectocervix, approximately one-third of CD45+ mononuclear cells consist of T cells, which have the ability to form lymphoid aggregates [98]. Menopausal changes in vaginal microbiota and the alteration in immune response occurring with menopause may predispose to local inflammation [99–101], resulting in an overall increase in inflammatory cytokines and chemokines, phenotypic changes in antigen presenting cells, maturation and activation of monocyte-derived dendritic cells, and increased number and activation of mucosal CD4+ T cells [102]. For women affected by rheumatic diseases, there is still limited evidence and understanding of the potential interplay between vaginal microbiota and systemic autoimmunity. Emerging data, in particular on SLE and Sjogren's syndrome [103, 104], suggest that this connection is relevant. An alteration of the vaginal microbiota was reported in SLE compared to healthy controls; patients showed significant differences in microbial composition, unaffected by treatment. Specific bacterial genera, including *Bacteroides*, *Escherichia-Shigella* and *Streptococcus*, seem able to distinguish SLE patients from healthy controls, potentially acting as biomarkers of the disease, and have been associated with immunological features of SLE, in particular *Escherichia-Shigella* proved negatively associated with serum C4 [104]. In Sjogren's syndrome, dysbiosis of the gut, oral, and vaginal microbiome has been described, with reduced richness compared to healthy controls. Only six genera showed lower relative abundance, and this proved associated with clinical characteristics as dry mouth and increased serum levels of immunoglobulins A and M. The microbiota diversity significantly increased after treatment with hydroxychloroquine, suggesting that bacterial composition and its variation as those occurring in menopause may influence the disease, and vice versa immunomodulatory treatment may restore a healthy microbiota [103]. It remains to be clarified whether and in what extent these local changes contribute to the development of an imbalanced immune system, autoimmunity, and modification of the course of an established rheumatic disease.

**Fig. 3** Schematic representation of the pathways potentially involved in the development or worsening of autoimmunity in menopause



Females are more at risk of autoimmune diseases and therefore an intriguing hypothesis involves the X chromosome. As previously described, its alterations are responsible for POI, with this condition being tightly associated with the development of autoimmune diseases. Both POI and autoimmune diseases may share underlying immune system dysregulations, often linked to genetic factors, like those on the X chromosome. Indeed, diseases like Turner syndrome, which involves X chromosome monosomy, are associated with both POI and autoimmune diseases, suggesting a common immunological pathway sustained by genetic background. In this context, the concept of escape from X-inactivation may need to be reconsidered. Indeed, as females have a XX genotype and males have a XY genotype, every cell in the female body epigenetically silences one of its two X chromosomes, to obtain a similar gene expression between females and males. However, around 15% of X-linked genes escape this silencing, leading to increased expression of certain gene products. This is particularly relevant since X chromosome encodes for many genes involved in immune regulation and potentially involved in autoimmunity, such as Toll-like receptors (TLR), in particular TLR7, FOXP3, a transcription factor for regulatory T cells, CD40L (CD154), important for immunoglobulin class switching, and CD132 (IL-2Rc), the gene responsible for the X-linked severe combined immunodeficiency [105, 106]. The molecule responsible for X-silencing is the long non-coding RNA Xist, which is transcribed only from the inactive X chromosome, and thus not expressed in males. Altered X-chromosome inactivation has been described in some autoimmune diseases [107–116], with changes in the expression of genes interacting with

XIST RNA in specific immune cells. Xist binds with various proteins, including tissue-specific proteins, to create a ribonucleoprotein (RNP) complex. Many of the proteins associated with Xist are known autoantigens and although the cause of the development of specific autoantibodies has been attributed to exposure of nucleic acid-protein complexes in the extracellular space, recent studies suggests that XIST RNP is an antigenic structure unique to females. This finding is highly relevant, considering that every cell in a woman's body contains XIST. Therefore, when any cell dies, for instance following tissue injury, XIST RNP is released in the extracellular space, potentially leading to immune sensitization to these antigens over time, resulting in the development autoantibodies. This process may explain, at least in part, the higher prevalence of autoimmune diseases in women compared to men, particularly connective tissue diseases that are associated with autoantibodies targeting XIST RNP. Another supporting factor for this is the presence of atypical B cells, also known as age-associated B cells, which accumulate as a result of Xist RNP expression. In fact, these B cells are enriched in human or mouse B cells that escape X inactivation and re-express TLR7 [117]. Atypical B cells are a distinct B cell population that expands with aging, during certain infections (such as malaria, HIV, and COVID-19), and in autoimmune diseases that are more common in females, such as SLE and RA. They accumulate in aged female mice but not in age-matched male mice, as a consequence of elevated TLR7 signalling [110]. Thus, atypical B cells represent an immunological link between aging, self-reactivity to Xist RNP, and escape from X-inactivation [117]. This mechanism suggests that on a predisposing

genetic background with prolonged exposure to XIST RNP, the impact of aging and menopause-related pro-inflammatory changes may all promote a pro-inflammatory and auto-reactive polarization of immune cell function, leading to menopause-related female autoimmunity and rheumatic symptoms (Fig. 3). This hypothesis highlights the gaps in our understanding the impact of menopause and emphasize the need for further research in this field.

## Conclusions

An increasing number of studies have explored the role of sex on the immune system, and there is a considerable amount of evidence in the literature suggesting that oestrogens play a significant part in autoimmunity [118]. However, there are limited data on the impact of menopause, although this may be a promising field and an ideal natural model to understand how hormones impact the immune system and the clinical phenotype in rheumatic conditions. Of particular relevance from the immunological perspective are women with premature ovarian insufficiency or late-onset-menopause. These two conditions, representing the opposite extremes of the fertility curve, offer a unique opportunity to investigate immune changes associated with oestrogen loss. As described in this review, menopause can induce the development of autoimmunity and can alter the course of immune-rheumatic diseases. The changes observed during menopause suggest an important role of hormonal fluctuations in modulating the immune system.

Several aspects need to be investigated and evaluated to fully elucidate the pathways involved and to define potential targets for personalized and precision medicine strategies. The study of the potential link between immune cell polarization, development of autoantibodies and hormonal modifications in menopause may disclose relevant etiopathogenic mechanisms, potential biomarkers, and therapeutic targets for an optimal management strategy to maximize quality of life in this critical phase of women's life.

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**Data Availability** No datasets were generated or analysed during the current study.

## Declarations

**Competing Interests** The authors declare no competing interests.

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