The Impact of Menopause on Immune Senescence

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Abstract: Several lines of evidence suggest that ovarian steroids modulate immune function in women. Women are at higher risk of autoimmune disease than men; generate more robust humoral responses to vaccination than men; and plasma cytokine levels and the immune response to certain vaccines change throughout the menstrual cycle. Aging is accompanied by a decline in immunity referred to as “immune senescence” that significantly contributes to increased morbidity and mortality in the elderly. Aging is also associated with menopause, one of the most dramatic age-related physiological changes in women. Given the strong evidence for sex differences in immune function between pre-menopausal adult women and men, it has been suggested that the loss of ovarian steroids associated with menopause might contribute to decreased immune function in post-menopausal women. However, we do not yet fully understand the interplay between ovarian and immune senescence. In this article, we review studies that have investigated the impact of menopause and hormone therapy on changes in immune function.

Keywords: Immune senescence, menopause, T cells, B cells, cytokines, estrogen, progesterone.

INTRODUCTION

Data from several studies indicate that sex hormones modulate immunity. These findings suggest that the loss of ovarian steroids associated with menopause might contribute to decreased immune function observed in aged post-menopausal women. However, very few studies have examined this question. Consequently, the impact of menopause and hormone replacement therapy on immune function remains poorly understood. In this article, we begin by reviewing gender differences in the immune response to infection and vaccination. Then, we examine the effect of ovarian steroids on lymphocyte function. This is followed by an overview of the age-related decline in immunity referred to as immune senescence. Then, we summarize the effect of menopause and combined hormone therapy (HT) on immune cell frequencies and cytokine production. We conclude with a discussion of examples of diseases that illustrate the interactions between menopause and immune senescence.

MODULATION OF THE IMMUNE RESPONSE TO INFECTION/VACCINATION BY OVARIAN STEROIDS

Data from several studies have shown sex differences in the immune response to infection (summarized in Table 1). For example, heart disease (myocarditis) after infection with coxsackievirus occurs more often in men than women [1]. Similar sex differences are seen in a mouse model where coxsackievirus infection causes more severe disease in male and pregnant female mice as compared to non-pregnant females [2]. Moreover, viral associated disease is mitigated in castrated or estrogen treated male mice [2]. Data from murine studies suggest that estrogen promotes a Th2 type response following coxsackievirus infection rather than a CD4 Th1 cell response, which is normally seen in males and associated with the development of myocarditis [2]. Hanta virus infections are also more prevalent in men than women and this sex difference is apparent only after puberty, suggesting a protective role of ovarian steroids [2]. Adult women also generate a more robust cell mediated response than men following cytomegalovirus (CMV) infection with higher IFNγ and interleukin (IL) -2 production [3]. Moreover, men are at greater risk for bacterial infection and sepsis after trauma, and experience greater mortality even after adjusting for age and disease severity (reviewed by Marriott et al) [4]. This difference in survival is most likely mediated by a difference in cytokine production [4]. Whereas male patients produced high levels of the Th1 cytokine tumor necrosis factor alpha (TNFα) during sepsis, female patients produced higher levels of the regulatory cytokine IL-10 [5]. Similarly, males are at a greater risk for major infections after surgery, a result attributed to a higher inflammatory cytokine response [6].

Sex differences have also been detected during HIV infection. Women have been shown to have higher CD4 lymphocyte counts than men throughout infection and lower viral loads early during infection [7]. In addition, it has been found that in vitro stimulation of peripheral blood mononuclear cells (PBMC) with HIV-1 antigens that stimulate the innate immune toll-like receptor 7 (TLR-7) on plasmacytoid dendritic cells (pDCs) resulted in higher interferon-α (IFNα)
production by women than men [8]. This in turn, induced a stronger secondary activation of CD8+ T cells, which is consistent with HIV+ women having higher levels of CD8+ T cell activation than men with equivalent viral loads [8]. Interestingly, HIV+ postmenopausal women have lower CD4 lymphocyte counts three years after seroconversion than women of reproductive age [7], again suggesting an immuno-stimulatory effect of estradiol.

Parasitic infections also show a strong sex bias with higher prevalence of infection and disease severity in men compared to women [9]. The resistance by females to parasitic infections correlates positively with estrogen concentrations [9]. As an example of the influence of estrogen, female mice, which are less susceptible than males to *Paracoccidioides brasiliensis* produce Th1 type cytokines in response to infection while males produce Th2 type cytokines [10]. However, when castrated male mice are treated with 17β estradiol (E2), their spleen cells produced higher levels of IFNγ and lower levels of IL-10 following stimulation with *Plasmodium brasiliensis* compared to control males, consistent with a more protective Th1 response observed in intact females [10]. Similarly, ovariectomized (OVX) mice treated with E2 produced higher levels of IFNγ and IL-10 (associated with a protective response) as well as higher antibody responses after *Plasmodium chabaudi* infection compared to OVX mice treated with placebo [11]. OVX mice receiving E2 also experienced less weight and hematocrit loss, as well as less hypothermia following malaria infection than OVX mice receiving placebo [11]. Finally, E2 treatment induces resistance to *Toxoplasma gondii* infection in both female and male mice [9].

As described for infections, women also generate a more robust response to most vaccines as evidenced by higher rates of seroconversion and lower rates of disease after vaccination than men [12, 13]. In an influenza vaccine trial, participants aged 18-49 and 50-64 were given either a full or half dose of vaccine. Women within the younger age group who received a half dose developed an equivalent antibody response as men who received the full dose of vaccine. Women in the older age group receiving a half dose had slightly lower responses than men in the same age group receiving a full dose [14]. Unfortunately this study did not look at women’s menopausal status, but these observations strongly suggest that the sex difference in the magnitude of the antibody response to influenza vaccine diminishes with post-menopausal status. Similarly, vaccines against HSV-2 also show sex differences in immunogenicity and efficacy. Early vaccine formulations showed some protection in women (26%) and no protection in men (-4%) [15]. More recently, a glycoprotein D subunit vaccine resulted in 73 to 74% protection in HSV negative women although protection in men remained negligible (11%) [16, 17]. Data from studies using a mouse model of HSV-2 challenge strongly suggest that this gender difference in protection is mediated by E2 [18]. In contrast to intact female mice, OVX vaccinated females experienced the same rate of infection as unvaccinated controls following challenge; however, E2 treatment of intact or OVX mice enhanced protection and decreased disease severity [18]. Interestingly, antibody titers in E2 treated mice were not significantly higher than those observed in untreated mice, but the neutralization potential was significantly improved [18].

Along with the heightened immune response to vaccines, women consistently report experiencing greater adverse reactions to a number of vaccines including 17D, Influenza, MMR, and HSV2 than men [13, 19]. This would be consistent with a more vigorous immune response to the vaccine. Indeed, following Yellow Fever vaccination, gene expression of TLR-associated genes that activate the interferon pathway, was considerably higher in women than men in the first ten days after vaccination [13]. This increased gene expression would be predicted to result in higher levels of inflammation and potentially adverse reactions.

Additional data that support the modulation of immune response by female sex hormones come from cross-sectional clinical and animal studies, which show that cytokine production by peripheral blood T cells varies throughout the menstrual cycle. Specifically, the number of PBMC able to...
secr`es IL-4 in response to phytohaemagglutinin (PHA) stimulation correlate with estrogen levels [20] and serum levels of the cytokines IL-6, IL-1β, IL-10, and IL-8 peak during the follicular phase when estrogen levels are highest [21-23]. Moreover, several lines of evidence suggest that E2 enhances the immune response whereas progesterone dampens it. For instance, the severity of systemic lupus erythematosus (SLE) and myasthenia gravis tend to be exacerbated after E2 treatment [24, 25]. On the other hand, the severity and incidence of rheumatoid arthritis and multiple sclerosis are decreased during pregnancy [26] when circulating levels of progesterone are high.

Similar immunomodulatory observations were made during infection. Prolonged exposure to progesterone in the form of the contraceptive Depo-Provera (Depo) increases susceptibility of female mice to HSV-2 genital infection [27]. Similarly, Depo treatment increases susceptibility of nonhuman primate females to a variety of sexually transmitted diseases including Chlamydia [28], SIV [29] and SHIV [30]. Clinical studies also found associations between Depo and chlamydia, HSV-2, HIV and HPV incidence in adult women [29, 31-33]. In contrast to Depo treatment, E2 administration to ovariectomized (OVX) female mice protected them from HSV-2 infection [34]. Similarly, female rhesus macaques treated with estrogen were protected from SIV transmission [35]. Interestingly, vaccination studies in humans indicate that vaginal immunizations might be more effective for induction of genital tract antibodies if performed during the mid-follicular phase of the menstrual cycle [36]. These observations strongly suggest that progesterone inhibits whereas E2 enhances the development of protective immunity [27, 34, 37, 38].

MECHANISMS OF ACTION OF OVARIAN STEROIDS ON LYMPHOCYTE FUNCTION

Ovarian steroids can modulate T and B cell function directly through binding of sex steroid receptors expressed by lymphocytes. Estrogen receptors are nuclear and there are two subtypes: α and β, which form homo and heterodimers [39]. The expression of ERα has been reported on lymphocytes, dendritic cells, macrophages, monocytes, natural killer cells, and mast cells ([40-46] and Fig. 1). ER expression on lymphocyte precursors is dependent on both age and stage in the cells’ development [47]. For example, CD4 T cells express higher amount of ERα than ERβ while B cells express more ERβ than ERα [46]. CD8 T cells and monocytes express only low amounts of both receptor types [46]. Variation in expression levels of ERs may contribute to immune function. For instance, PBMC from SLE patients showed significantly increased levels of ERα mRNA and significantly decreased ERβ mRNA compared to healthy controls. Additionally, the decrease in ERβ was significantly inversely correlated to the patients’ Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores [48]. Also, as will be discussed later, the function of CD4 T cells and B cells, which have higher levels of ER expression than CD8 T cells, are also more influenced by estrogen.

Estrogen treatment of B cells increases the expression of the anti-apoptotic molecule Bcl-2 thereby potentially increasing the resistance of auto-reactive B cells to apoptosis ([49-51] and Fig. 1). Estrogen also enhances B cell activation [52], IgG production [53], and upregulates activation-induced deaminase (AID), thereby enhancing somatic hypermutation frequency and class-switch recombination resulting in greater antibody affinity-maturation ([54] and Fig. 1). As described for B cells, E2 was shown to inhibit activation-induced apoptosis of T cells from SLE patients by down-regulating the expression of Fas ligand, which may allow for the persistence of autoreactive T cells [55]. In vitro studies examining the effect of E2 on T cell proliferation and cytokine production have often yielded contradictory results when using PBMC [56] although some observations do suggest a potential bias towards Th2, Th17 [57] and Treg polarization in E2 treated T cell cultures [58] (Fig. 1).

Ovarian steroids can also modulate adaptive immune responses indirectly by acting on cells of the innate immune system that in turn regulate the activation and differentiation of lymphocytes. For example, E2 regulates TLR2 expression on lipopolysaccharide (LPS) stimulated microglial cells in vivo [59]. While intact mice display an increased expression of TLR2 at 24 hours after both intracerebral and systemic LPS stimulation, this is not the case in OVX mice, and this outcome is reversible by the administration of E2 [59]. Further experiments using both ERα knock out (ERKO) and ERβ knock out (BERKO) mice, established ERα as the key receptor for the expression of TLR2 [59].

A recent study showed that presence of estrogen related receptor alpha (ERRα) was required for IFNγ production and efficient clearance of Listeria monocytogenes by macrophages [60]. Moreover, E2 administration significantly increases mRNA for the inflammatory cytokines IL-1β, IL-6, and TNFα as well as inducible NO synthase in macrophages from thioglycollate injected OVX mice via an ERα dependent mechanism [61]. Human dendritic cells matured in the presence of E2 and TNFα, but not TNFα alone, promote the differentiation of naïve CD4 T cells into Th2 cells [62]. However, E2 matured human dendritic cells have been shown to possess a decreased capacity for stimulating T cell proliferation [64]. Mouse pDCs stimulated with CpG in the presence of E2 also have higher expression of the costimulatory molecules CD40 and CD86 as well as higher IFN-α production [63]. When co-cultured with B cells, these E2 treated pDCs increase B cell viability, but not proliferative capacity [63].

Progesterone receptors (PR) are not as ubiquitous as ERs and no nuclear PR have been detected in PBMC ([39] and Fig. 1). T cells do however express membrane bound progestosterone receptors α and β [65]. The expression of PRα is also upregulated on CD8+ T cells during the luteal phase of the menstrual cycle [65]. Adding to the complexity of the effects of sex steroids, PR are primarily induced by estrogen via ER creating a complex interaction between these two hormones [39]. Natural killer cells and monocytes are the only other immune cell types to express PRs [39]. Like ER, progesterone receptors function as transcription factors by binding to progesterone responsive elements (PRE) upon ligation or by binding to other transcription factors [39]. Recent studies showed that progesterone treatment reduces the ability of dendritic cells to take up antigenic peptides, stimulate T cell responses [66], and secrete the potent antiviral cytokine
IFNα [67]. Thus, as described for E2, progesterone modulates lymphocyte function both directly and indirectly by acting on innate immune cells (Fig. 1).

**IMMUNE SENESCENCE**

Aging is associated with a general decline in immune system function, commonly referred to as ‘immune senescence,’ that has been proposed as prognostic factor for human longevity [68]. This progressive deterioration affects both innate and adaptive immunity, although accumulating evidence indicate that the adaptive arm of the immune system exhibits more profound changes [69]. Longitudinal clinical studies have identified a cluster of immunological changes that are associated with immune senescence [70]. The most prominent change is a severe loss of naïve T cells and a shift towards memory phenotype T cells especially oligoclonal effector memory cells, which results in the shrinkage of the T cell repertoire and the loss of T cell proliferative ability. This loss of naïve T cells is driven by thymic involution and the exhaustion of naïve T cells. Furthermore, aging is accompanied by a decrease in CD4/CD8 T cell ratio and a decrease in B cell numbers in PBMC [68]. Aging is also accompanied by an age-dependent upregulation of circulating pro-inflammatory cytokines, notably IL-6 and TNFα [71, 72]. This chronic inflammatory state is believed to significantly contribute to the development of age-related diseases such as Alzheimer’s, atherosclerosis, sarcopenia, diabetes, rheumatoid arthritis and certain types of cancer [73].

![Fig. (1). Estrogen and Progesterone receptor expression pattern and impact on immune cells.](image)
In women, aging is accompanied by a dramatic loss in ovarian function and subsequent menopause around the age of 50. Thus, with the average life span of ~80 years, women can expect to spend a significant portion of their lives in a post-menopausal state. The endocrine changes associated with entry into menopause appear to result from the age-related depletion of follicular reserve. Decreasing numbers of developing follicles leads to a failure to produce the hormonal support necessary to maintain levels of inhibin B. The decrease in inhibin B production results in deregulated production of follicular stimulating hormone (FSH), which in turn results in altered estrogen production and eventually a decrease in the levels of circulating estrogen [74]. This diminished responsiveness results in a cycle that culminates in menopause [75]. Menopause not only affects women's fertility, but also exacerbates several age-related diseases such as osteoporosis, cardiovascular disease, loss of cognitive abilities and the incidence of some cancers [76, 77].

Given that ovarian steroids modulate immune function in adult women, it is likely that the loss of ovarian steroids that occurs with menopause could have a detrimental effect on immune function in post-menopausal women [78, 79]. This hypothesis is supported by the observation that rhinovirus infection induces a higher IFNγ and IL-13 response in women than men, however this sex difference is no longer detected after the age of 50 [80]. Similarly, hepatitis vaccines induce higher antibody titers and seroconversion rates in adult women, but this sexual dimorphism is no longer evident in vaccinees over the age of 60 [13]. The incidence of herpes zoster is also higher in women aged 50 years of age compared to males [81, 82]. Finally, studies from our laboratory have shown that OVX female rhesus macaques generate reduced T and B cell responses to vaccination compared to age-matched intact animals. Specifically, T and B cell proliferative bursts were delayed and reduced in magnitude in OVX animals. Consequently IgG titers and frequency of IFNγ+ T cells was significantly reduced in OVX animals [83].

Moreover, some of the age-related chronic diseases, notably osteoporosis and atherosclerosis, are also exacerbated by menopause [84], thereby establishing a complex interaction between immune senescence and menopause. However few studies have investigated the impact of menopause and hormone therapy on response to vaccines.

THE IMPACT OF MENOPAUSE ON IMMUNE CELL FREQUENCIES

Changes in lymphocyte numbers that occur with the onset of menopause are not entirely clear (Fig. 2). Some studies have reported a significant decline in total lymphocyte numbers [85], while others report no change [86]. However, postmenopausal HT users were found to have significantly higher lymphocyte percentages than nonusers, and new users

![Fig. (2). Modulation of immune cell frequency and cytokine production/levels by age, menopause and hormone replacement therapy.](image-url)
experienced a significant increase in their lymphocyte percentage after just one to six months on HT [86].

One of the most conserved age-related changes is the decrease in the percentage of naïve T cells and the accumulation of memory T cells. There is significant decrease in naïve T cells and an increase in memory and activated T cells between early and late menopause and the use of HT has no effect on these changes, suggesting that chronological age has a more significant impact on loss of naïve T cells than menopause [86-88]. Another hallmark of T cell senescence is a reduced CD4/CD8 ratio [68]. Data from a few studies suggest that menopause decreases the CD4/CD8 ratio by decreasing the frequency of CD4 T cells [79, 85]. Since, women of reproductive age have more CD4 T cells and respond more vigorously to infection/vaccination than men [89, 90], menopause-associated loss of CD4 T cells could be one of the mechanisms by which ovarian senescence contributes to immune senescence.

Total B cell numbers also decline with age and with menopause [85]. B cells can be broadly divided into B1 and B2 cells and their frequency is altered with increasing age [91]. B1 cells produce predominantly non-specific binding IgM whereas B2 cells, or conventional B cells are involved in the adaptive humoral immune response. The reduction in B cell numbers through menopause appears to be isolated to the B2 cells, which are significantly lower in late menopause compared to early and perimenopause [92]. Furthermore, B2 cells are significantly higher in HT users than non-users [92]. These studies suggest that menopause leads to a reduced humoral response and this change can potentially explain the disappearance of sex differences in antibody responses following infection and vaccination [13, 14, 80]. Similarly, total abdominal hysterectomy and oopherectomy in adult women results in a decrease in circulating B cells and CD4/CD8 ratio, and an increase in the percentage of NK cells [93]. All these changes are consistent with immune senescent phenotype.

The number of NK cells do not appear to be affected by natural menopause, but do increase with premature menopause [85] and surgical menopause [93] potentially as a compensatory mechanisms for T cell associated changes. Peripheral blood monocytes increase after menopause [94], but the number of tissue specific macrophages in the ovary diminish [95, 96]. To our knowledge, frequency and function of dendritic cells before and after menopause have not been studied.

Several laboratories investigated whether hormone therapy could reverse changes in circulating lymphocyte frequencies observed in post-menopausal women. Estrogen therapy reverses the decrease in CD4 and B cells and the increase in NK cells that is seen in patients who have undergone a hysterectomy [85, 93]. Similarly, combined hormone therapy reverses the age-related decrease in number of circulating B cells and T cell proliferative potential in post-menopausal women [97] and leads to an increase in B2 B cells [92]. Furthermore, estrogen has been shown to decrease the number of CD8 T cells in post-menopausal women thereby increasing the CD4/CD8 ratio [98], and to restore the levels of circulating monocytes to levels seen in cycling women [94].

MODULATION OF CYTOKINE LEVELS AND PRODUCTION BY MENOPAUSE AND HORMONE THERAPY

The impacts of menopause and hormone therapy on cytokine production and plasma levels are equally complex (Fig. 2). Aging is associated with an increase in circulating inflammatory cytokine levels notably IL-6 and TNFα, a process often referred to as inflamm-aging, and believed to contribute to the development of several chronic diseases such as sarcopenia, Alzheimer’s, osteoporosis and certain types of cancer [99-101]. In one cross-sectional study both IL-6 and soluble IL-6 receptor were significantly higher in postmenopausal than premenopausal women and median IL-6 levels were found to be tenfold higher in centenarians than premenopausal women [99]. Similarly, IL-6 production after in vitro stimulation also increases with age. More specifically, in vitro stimulation of PBMC with LPS shows the highest production of IL-6 as well as TNFα and IL-1β in women aged 52 to 63 as compared to young adult women [101]. Interestingly, IL-6 production by LPS stimulated PBMC is higher in women taking an estrogen plus continuous progestin regimen but not in women receiving estrogen only, compared to nonusers [102]. Similarly, women receiving transdermal estrogen experienced a significant decrease in IL-6 serum levels after three months of treatment compared to post-menopausal women who did not [103]. Indeed, serum IL-6 levels show a negative correlation with serum estrogen levels in users [103] and in women spanning the transitional stages of menopause aged 40 to 65 years [100].

A trend towards an increase in serum IFNγ levels during early menopause (< 5 years post menopause) followed by a slight decrease in late menopause has been reported [100]. Similarly, IFNγ production in whole blood or PBMC in response to either PHA or LPS stimulation in vitro, begins to increase at around the age of 40 and peaks during early to mid menopause before again decreasing during late menopause [104-106]. Previous in vitro studies have shown that estrogen has a biphasic effect on IFNγ production by LPS stimulated whole blood samples, with low levels of estrogen stimulating and high levels inhibiting production [107]. Therefore, it is possible that as estrogen levels decrease during early menopause, it stimulates an increase IFNγ production before becoming too low during menopause to have an effect [108]. IFNγ serum levels decreased in perimenopausal women who have had a bilateral salpingo-oopherectomy and increase once estrogen treatment is initiated [93]. On the other hand, combined hormone therapy is associated with lower IFNγ production probably due to the opposing effect of progesterone [105, 106].

A transient increase in serum IL-2 occurs in women within the first five years of menopause has been described and the data suggest a weak negative correlation with serum estrogen levels [100]. Similarly, IL-2 production following LPS stimulation of whole blood cultures increases with age, peaking during early menopause, and then declines [105]. HT reduces plasma IL-2 levels, albeit not significantly as well as IL-2 production by T cells following stimulation of purified PBMC with PHA, an approach that specifically targets T cells [106]. Another study found that transdermal administration of estrogen does not change IL-2 plasma levels.
The difference in the impact of menopause on plasma IL-2 levels between these studies may have been a result of the route of estradiol administration. Transdermal administration may not increase estrogen plasma levels enough to have an effect on IL-2 production. Alternatively, increased IL-2 levels following oral administration of estrogen could be due to hepatic first-pass effects such as increased CRP levels, which are not observed during transdermal administration of estradiol. IL-4 plasma levels were reported to increase after menopause and HT reverses this increase [100, 109]. Conversely, oophorectomy decreases IL-4 levels but ET did not affect this decrease [93]. In PHA stimulated whole blood IL-4 production does not increase until mid menopause and then becomes significantly lower in late menopause [105].

Serum TNFα levels were reported to increase after menopause in some studies [109, 110] while other studies reported no changes in serum TNFα levels [100]. HT reduced TNFα levels [109]. Similarly, data from some studies suggest that menopause is associated with increased plasma IL-1β levels and that HT reverses this increase [109], while other studies report only a transient increase in circulating IL-1β [100]. The impact of menopause on IL-10 and IL-12 is equally controversial with some studies reporting an increase [105, 109], while others report no change [100] or a decrease in these cytokines [110]. HT and transdermal estrogen do not seem to have an impact on IL-10 levels [103, 109]. A negative correlation of IL-8 with estrogen level was reported in both humans and mice [100, 111].

INTERPLAY BETWEEN OVARIAN AND IMMUNE SENESCENCE AND OSTEOPOROSIS

It has long been known that post-menopausal osteoporosis is estrogen dependent. It is only during the last decade however, that the role of the adaptive immune system in this process has been discovered. It is part of a complex chain of events that begins with estrogen deprivation resulting from the cessation of ovarian function. Estrogen bound to its receptor can target estrogen receptor elements in the promoter region of some genes, thereby modulating their expression [112]. One such gene is transforming growth factor beta (TGF-β), a well-known negative regulator of immune function [113]. Estrogen deprivation results in reduced transcription of TGF-β, which in turn leads to increased T cell proliferation and differentiation [114], and increased levels of TNFα and IL-1, two key players in bone loss [115, 116].

Moreover, increased T cell activity results in elevated levels of IFN-γ [114, 117], which activates MHC class II transactivator (CIITA) leading to greater expression of MHCII on antigen presenting cells [113, 118]. Greater numbers of memory cross-reactive CD4 T cells are thereby activated [118] resulting in increased TNFα production within the bone marrow and not in PBMC [113, 118, 119]. The increase in IFN-γ levels under the condition of estrogen deficiency promotes osteoclasts due to the presence of higher levels of TNFα, [117] which increase receptor activator of nuclear factor kappa-B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) expression as well as directly stimulate osteoclast activity [113, 118].

Another cytokine that increases dramatically with estrogen deprivation is IL-7 due in part to lower levels of TGF-β [118]. IL-7’s role in osteoporosis has been controversial. This may be because as with IFN-γ, the effects are indirect through action on T cell proliferation. Indeed, T cell deficient mice are protected from OVX induced bone loss [120] and Toraldo et al., showed IL-7 to induce OVX bone loss through a T cell dependent manner in vivo [121]. Ryan et al. take things a step further showing IL-7 increase of thymic T cell output also contributes to estrogen deficient bone loss [122].

In summary, estrogen deficient bone loss is the result of complex and often redundant pathways involving many dif-

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Fig. (3). The interplay of menopause and immune senescence in osteoporosis.
different cytokines that offer many opportunities for potential therapies (Fig. 3). However, to date HT is the only well established effective treatment. Interestingly, studies by Vural and colleagues found that just two months of HT decreased plasma TNFα and IL-1b levels, and urinary hydroxyproline and calcium excretion to a pre-menopausal level [109]. These observations suggest that the mechanism by which HT exerts its bone protective effect is by reducing inflammatory cytokine production. Since menopause contributes to inflaming, it may over time increase the expression of osteoclastogenic cytokines by T cells, which in turn exacerbates postmenopausal osteoporosis. This hypothesis that inflaming is “responsible in great part for postmenopausal osteoporosis” was recently put forth and highlights the complex interplay between immune and ovarian senescence [123].

CANCER INCIDENCE CAN BE MODULATED BY MENOPAUSE

Risk for some cancers in women also change with the onset of menopause [124, 125]. One such cancer is hepatocellular carcinoma (HCC), a complication of chronic hepatitis C (HepC) infection [126]. Men are 3 to 5 times as likely to develop HCC than women, [126] and progression of HepC associated fibroses, a risk factor for HCC, is also higher in men as well as post-menopausal women not receiving HT compared to pre-menopausal women and postmenopausal women receiving HT [127, 128]. Naugler et al. showed that estrogen had a protective effect in male mice against chemically induced HCC and that the lack of ERα increased injury in female mice [126]. Humans that develop HepC cirrhotic associated HCC are more likely to have low hepatic levels of ER [129]. Estrogen inhibits IL-6 and this appears to be the key mechanism of protection [126]. In humans, both circulating and intrahepatic levels of IL-6 are higher in men and postmenopausal women compared to premenopausal women [130]. Additionally, HCC incidence was decreased and survival time increased in male IL-6 KO mice [126]. Additional studies suggest that HT may also reduce the risk of colorectal cancer [131].

CONCLUDING REMARKS

Although improvements in healthcare have led to an increase in lifespan, the age at which women enter menopause has remained relatively constant at approximately 50 years of age. Thus, with an average life span of about 80 years, women can expect to spend over one third of their lives in a post-menopausal state. Ovarian steroids have a regulatory function in several body systems and the menopause-induced decline in the levels of these steroids is likely to trigger many pathophysiological changes. One such system is the immune system, which itself undergoes significant remodeling with age. Data from several studies suggest that both natural and surgical menopause are associated with the development of immunosenescent changes and that hormone therapy can delay and/or reverse some of these changes (decreased CD4:CD8 ratio, decreased B cell frequencies and increased inflammatory cytokine levels), which in theory should result in improved immunity in post-menopausal elderly women. However, our understanding of the interplay between ovarian and immune senescence remains rather limited. A better understanding of the pleiotropic effects of ovarian steroids on immune function has important implications for women’s health. Therefore more careful studies that take into account the stage of menopause in addition to other physiological parameters such as metabolic syndrome should be conducted to address this critical question.

CONFLICT OF INTEREST

None declared.

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REFERENCES


Kamada M. Transient increase in the levels of T-helper 1 cytokines in postmenopausal women and the effects of hormone replacement therapy. Gynecol Obstet Invest 2001; 52(2): 82-8.


Abu-Taha M. Menopause and ovariectomy cause a low grade of systemic inflammation that may be prevented by chronic treatment with low doses of estrogen or losartan. J Immunol 2009; 185(2): 1393-402.


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Codes L. Liver fibrosis in women with chronic hepatitis C: evidence for the negative role of the menopause and steatosis and the potential benefit of hormone replacement therapy. Gut 2007; 56(3): 390-5.

