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The Immune System in Menopause: Pros and Cons of Hormone Therapy

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Abstract

With aging, a general decline in immune function is observed leading to immune-senescence. Several of these changes are gender specific affecting postmenopausal women. Menopause is a normal part of a woman's lifecycle and consists of a series of body changes that can last from one to ten years. It is known that loss of sex hormones due to aging results in a reduction of immune functions. However, there remains a major gap in our understanding regarding the loss of immune functions particularly in the female reproductive tract (FRT) following menopause and the role of menopausal hormone therapy (MHT) in protecting against immune senescence. The current review presents an overview of changes in the immune system due to aging, focusing on genital tract immunity in menopausal women and the risks and benefits of using MHT.

Keywords

female reproductive tract; menopause; menopausal hormone therapy; estrogen; progesterone; HIV; immunity

Introduction

Immunologically, aging is characterized by a general dysregulation of immune responses culminating in a gradual immune senescence of all cells. Aging is gender specific and is marked by "menopause" in women. Menopausal symptoms are variable among women and can include hot flashes, night sweats, sleeplessness, mood changes, loss of energy, loss of libido, vaginal dryness, and urinary symptoms. Usage of menopausal hormone therapy (MHT), estrogens, progestogen, or a combination of the two, relieves some of these

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symptoms. Although quality of life improvement has been reported for MHT users versus placebo, serious side-effects, especially upon long-term use, remain a concern [1].

Although systemic side-effects of MHT have been studied, details on its effects on the aging immune system are less clear. Particularly little is known about effects on the immune environment of the female reproductive tract (FRT). This article will focus on the effects of menopause and hormone therapy on the immune system, particularly in the FRT. Other aspects of menopause and hormone therapy are discussed elsewhere in this issue.

Immune system and Aging

The hallmarks for immune senescence include (i) immune profile, characterized by decreased CD4+:CD8+ T cell ratio, increased numbers of differentiated memory and effector T cells, depletion of naïve T cells and decreased frequency of B cells; and (ii) Inflamm-Aging, characterized by an increased inflammatory state with increased levels of pro-inflammatory cytokines. In consequence, aging of the immune system results in an increased susceptibility to infections and decreased response to vaccination [2], [3] [4,5]. Aging has been shown to impair responses to viral infections including Human Immunodeficiency Virus (HIV), Herpes Simplex Virus (HSV), Cytomegalovirus (CMV), and Influenza through multiple mechanisms including the functional impairment of plasmacytoid dendritic cells, the major producer of type I interferons and the main defense against viral infections [2].

The innate immune system, which is the first line of defense against invading pathogens, is altered with aging. Natural killer (NK) cells, which play a significant role in protection against viral pathogens and tumors, actually increase in number with age. However, they show decreased cytotoxicity and decreased ability to produce cytokines [6,7]. Chemotaxis, a hallmark of immune response, is dysregulated in neutrophils, monocytes/macrophages and dendritic cells. Phagocytosis by macrophages and dendritic cells (DC) and super-oxide production by neutrophils and monocytes/macrophages are reduced as well. DC show reduced capacity to present antigen thereby disrupting the ability of the innate immune system to activate the adaptive immune system. In addition, recognition by and signaling through the major innate pattern recognition receptor (PRR) families, toll-like receptor (TLR), NOD-like receptors (NLR), is also dysregulated in the aged [8,9].

The adaptive immune system is also compromised with aging. Studies with octogenarians and nonagenarians (OCTO and NONA studies respectively, [10,11] have associated aging and CD4+ and CD8+ T cells with impaired function and reduced ability to respond to pathogens [3]. Persistent viral infections, especially CMV, have been consistently detected in the aged and are considered to be biomarkers of immunosenescence [3]. B-cell function is also reduced in the elderly in that the ability to produce robust high affinity antibodies is impaired [3]. Age associated immune impairments result in predisposition to infections and poor vaccination responses [7,12,13,14,15] making them a high risk population and creating a need in the field to optimize therapeutics and vaccines specifically for the elderly.

Aging in women

Gender-specific decline in immune functions has been described. It is well-known that women are at a higher risk of developing autoimmune diseases, which indicates that certain disease conditions are mediated by sex hormones [16]. As multiple immune parameters are estrogen responsive, several patho-physiological conditions are altered by natural or induced changes in estrogen levels that vary with adolescence, menstrual cycle, pregnancy, menopause, as well as the use of corticosteroids, oral contraceptives (OC) and MHT. While this review, focuses primarily on the effects of estrogens on the immune system, it is important to recognize that progesterone, testosterone, and prolactin have all been implicated in affecting immunity in women [16].

An inflammatory state devoid of protective immune factors characterizes the immune microenvironment in menopausal women. Postmenopausal women show higher chronic levels of pro-inflammatory cytokines MCP1, TNFα, and IL-6 as well as a reduced ability to respond to pathogens or stimuli [16,17]. In addition to its role as a pro-inflammatory cytokine, IL-6 is also a key factor in bone reabsorption by osteoclast activation and also seems to be correlative with other diseases that have been associated with menopausal women such as diabetes, atherosclerosis and cardiovascular diseases [16]. CD4 T and B lymphocytes and cytotoxic activity of NK cells are typically decreased in postmenopausal women [16]. As a result, attenuated immune response and higher susceptibility to pathogenic invasion and infection are more common in this group.

Kumru *et al* [18] analyzed immune profile in blood from perimenopausal women who underwent total abdominal hysterectomy and bilateral salpingo-oopherectomy for uterine myoma (fibroids). One month after the surgery, an increase in CD8 T cells and decrease in B cells, CD4:CD8 T cell ratio and serum levels of IL-4 and IFN-γ were observed and, importantly, these effects were reversed by MHT. In a different study [19], blood analysis from postmenopausal women, relative to premenopausal women, showed decreased number of B cells and CD4 T cells, increased CD8 T cells and NK cells and generalized activation of the immune system. These immune alterations were also present in women with premature menopause included in the study, which showed reduction in total lymphocyte numbers and general immune activation compared to fertile women of the same age.

Effects of sex hormones on the immune system in the female reproductive tract

Sex hormones, estrogen (E_2) and progesterone are the master regulators of the immune system of the FRT. Estrogen exerts its biological effects via receptors estrogen receptor alpha (ER-α) and estrogen receptor beta (ER-β) which are differentially expressed in tissues and functionally distinct, often showing opposing effects [20]. Binding of estrogen to its receptors can regulate over 200 genes with distinct subsets affected by each receptor [21]. Most immune cells as well as epithelial cells and stromal cells throughout the FRT express estrogen and progesterone receptors and are responsive to sex hormones [22]. In addition to direct effects mediated through hormone receptors in immune cells, sex hormones act indirectly on immune cells through their actions on epithelial cells and stromal fibroblast secretion of growth factors [23]. For example, uterine epithelial cell proliferation and endometrial development is dependent on estradiol stimulation of underlying ERα-positive

stromal cells to produce growth factors such as HGF and KGF [24,25]. Ochiel *et al.* demonstrated that conditioned media, containing TGF-β from uterine epithelial cells suppressed differentiation and responses to TLR agonists in immature dendritic cells and also inhibited HIV trans-infection by immature dendritic cells [26,27]. Recently, potentially protective effects of 17β-estradiol have been demonstrated when treatment of CD4+ T cells and macrophages with E_2 prior to HIV challenge reduced their susceptibility to HIV infection in a dose-dependent manner [28].

Effects of hormone deprivation on the innate immune system in the female reproductive tract

In contrast to age-related changes in systemic immune responses, age-related immune responses in FRT of postmenopausal women remain mostly unknown. Considering that several reports demonstrate a lack of correlation between peripheral blood and the mucosal tissue [29,30], characterization of local responses becomes necessary [30].

Studies have demonstrated that innate immune factors are compromised in the reproductive tract of postmenopausal women [31]. As multiple immune factors of the FRT are estrogen responsive, the absence of estrogen with aging results in loss of TLR function, secretory antimicrobial components, commensal lactobacilli, and acidity of vaginal microenvironment [32]. The vaginal epithelium, which acts as a barrier against pathogens, thins significantly in the non-estrogenic postmenopausal state. There is also lack of production of cervical mucus, which itself is a protective barrier against pathogens [33]. Mselle et al [34] have shown that inactive endometrium has lower numbers of NK cells compared to endometrium of cycling women. Loss of specific endogenous broad-spectrum antimicrobials in the FRT of postmenopausal women has also been reported. Fahey et al [35] reported a loss of antibacterial activity against both Gram-positive and Gram-negative bacteria in the uterine secretions of postmenopausal women and correlated this with a loss of secretory leukocyte protease inhibitor (SLPI) secretion, a molecule well known for bactericidal as well as anti-HIV activity [35,36]. Shimoya et al [37] confirmed lower SLPI levels in cervical vaginal lavage (CVL) from postmenopausal women and further demonstrated that hormone replacement therapy in elderly women increased SLPI levels. More recently, we observed a reduction in anti-HIV activity in CVL from postmenopausal compared to premenopausal women (M. Ghosh, J. V. Fahey, S. Cu-Uvin, C. R. Wira, unpublished observations). Using ELISA and Luminex analyses we also found that postmenopausal CVL contained altered levels of pro-inflammatory cytokines including IL-6 (Ghosh, unpublished observation) when compared to premenopausal controls. This suggests that changes in innate immune components in FRT secretions might increase the risk of infection by HIV and other sexually transmitted infections (STI) in postmenopausal women.

Effects of hormone deprivation on the adaptive immune system in the female reproductive tract

Characterization of adaptive immune responses and the T-cell repertoire in the FRT of postmenopausal women are major gaps in knowledge. In premenopausal women, hormonal changes control architecture and function of T cells. Lymphoid aggregates can be found in the uterus, which change in size throughout the menstrual cycle [38]. These aggregates are

absent in postmenopausal women suggesting a role for estrogen and progesterone in their regulation [38,39]. Likewise, sex hormones regulate the activity of cytotoxic lymphocytes (CTL), the main cells involved in protection against intracellular pathogens, such as viruses. CTL activity in the uterus varies in intensity with the menstrual cycle in premenopausal women but is significantly higher in postmenopausal women relative to that seen at any point during the menstrual cycle [40,41]. In the cervix and vagina, however, CTL activity is independent of hormonal fluctuations and remains high throughout the cycle [40]. Regulatory T cell (Treg) expansion, responsible for immune-modulation and peripheral tolerance, is also under hormonal control. Compared to premenopausal women, in which numbers increase in the follicular phase and decrease in the luteal phase, postmenopausal women display low and constant numbers of Treg [42,43]. These findings suggest an increased immune activation state in the FRT of postmenopausal women.

Predisposition to infections and impaired vaccination responses in postmenopausal women

Increased susceptibility to infections affecting the FRT has been described in a number of studies. In postmenopausal women, a second peak in Human papilloma virus (HPV) prevalence has been reported [14,44]. A recent study demonstrated that weak proliferative responses in lymphocytes were associated with increased risk of HPV recurrence. New HPV infections in older women with no sexual activity, is thought to be due to reduced immune responses. [45]

HIV-1 infection is also increasing in postmenopausal women, mostly through heterosexual transmission [13]. A study conducted in Europe comparing HIV-discordant couples found that women over 45 had a 4-fold increased risk of acquiring HIV compared to women under 45 years of age [46]. Studies focused on cells from the FRT have found increases in HIV-coreceptors and activation markers on immune cells from postmenopausal women relative to that seen in premenopausal women [13]. Meditz et al. demonstrated higher percentage of CCR5+ CD4+ T cells in cervix from postmenopausal women than in premenopausal women within both the overall CD4+ T cell population as well as the activated population (HLA-DR+ CD38+). Moreover, a positive linear correlation was found between CCR5 expression and age. Whether this increase was related to hormonal or non-hormonal effects of aging could not be determined. Studies in macaques demonstrate increased susceptibility to Simian Immunodeficiency Virus (SIV) following ovariectomy. This was reversed by exogenous estrogen administration, strongly suggesting that hormone-related mechanisms were involved [47,48]. Another study reported increased HIV replication in ectocervical explants from postmenopausal women compared to premenopausal women, and this increase in infection was associated with an enhanced secretion of pro-inflammatory cytokines IL-6 and IL-1β in postmenopausal women [49].

An estimated 10 to 15 percent of women over 60 years of age suffer from frequent urinary tract infections [12]. In premenopausal women, beneficial commensal lactobacilli maintain low vaginal pH and produce lactic acid, thereby inhibiting colonization by uropathogens [50]. In the absence of sex hormones in the FRT following menopause, the lactobacilli are replaced by Enterobacteriaceae family which results in increased susceptibility of

postmenopausal women to urinary tract infections. Whereas some studies showed that intravaginal administration of estrogens prevented recurrent urinary tract infection in postmenopausal women, others have shown no effects [51,52]. Heinemann *et al* has also shown that in women on combination MHT, lactobacilli species was recovered in the vagina of postmenopausal women [12].

Aging is associated with poor vaccination responses [7]. Impaired vaccination responses in the elderly have been described against Influenza, Pneumococcus and Varicella zoster vaccines [7,15] making them a high risk vulnerable population. Studies in ovariectomized rhesus macaques, which display menstrual cycles and reach menopause the same way that women do, demonstrated an increase in terminally differentiated CD4 memory T cells, increased inflammatory cytokine production and diminished T- and B-cell immune responses to vaccination compared to intact animals. These effects are comparable to those observed in postmenopausal women where increased levels of inflammatory cytokines and reduced immune responses to infections and vaccines can be detected. Experiments conducted in macaques allowed to distinguish between the effect of age and the effect of hormonal deprivation and demonstrated that, regardless of age, the loss of sex hormones impairs immune responses. [53]

Effect of MHT on the immune system

Despite the evidence that endogenous sex hormones influence adaptive and innate immunity in younger females [54], the effect of exogenous sex hormones on immune function of postmenopausal women remains poorly understood.

Studies have demonstrated that MHT partially reverses the deleterious effects of aging on the immune system. Porter *et al*. [55] found that postmenopausal women on MHT displayed higher numbers of B-cells, lower proportion of activated CD4+ T cells and, importantly, improved T-cell function with enhanced ability to proliferate and increased TNF-α production compared to non-MHT users. Moreover, MHT reduced the elevated plasma levels of the pro-inflammatory cytokines TNF-α, IFN-γ and IL-6 detected in blood from postmenopausal women [56,57,58]. Another study found MHT usage to be associated with a significant decrease of NK cell cytotoxicity, IL-2 and IFN-γ production [59]. Kumru *et al*. [18] found a “postmenopausal” type immune profile in women undergoing hysterectomies and also observed a reversal of some of these effects upon MHT treatment. Whereas most of these studies were focused on women on combined hormonal therapy, Hanifi-Moghaddam et al [60] showed differential gene expression in when women were treated with estradiol, estradiol + medroxyprogesterone acetate or Tibolone.

The same study found differential clinical responses to MHT in the FRT when uterine and vaginal tissues from postmenopausal women were compared [60]. For example, proliferation and apoptosis were strongly up-regulated in endometrium with estrogen treatment alone, while the vagina was weakly responsive to hormones. Increased proliferation in endometrium induced by estradiol treatment was also demonstrated in a study evaluating the effects of selective estrogen receptor modulators (SERM) on tissue explants from pre- and postmenopausal women by evaluating number of Ki67-positive cells

[61]. This study found that whereas estradiol stimulated proliferation in premenopausal tissues by 55%, proliferation was increased by 250% in postmenopausal tissues. The SERM raloxifene, used to treat osteoporosis in menopausal women, enhanced proliferation in pre but not in postmenopausal tissues. However, the SERM tamoxifen, used to treat breast cancer, stimulated proliferation in only postmenopausal tissues. Our work has also shown that SERM treatment has a direct effect on the secretion of antimicrobial chemokines by mouse uterine epithelial cells. CCL20/MIP3α, a potent anti-HIV molecule [62], is significantly enhanced when mouse uterine epithelial cells are treated *in vitro* with SERM ICI 182780 or Y134 [22].

The effects of MHT on the FRT innate immune system was demonstrated by Shimoya *et al.* [37] showing decreased levels of SLPI in postmenopausal CVL which were enhanced in women on MHT. Differential regulation by MHT between upper and lower FRT was also recently described by Kumar et al [63]. Expression of SLPI, an innate immune molecule with antimicrobial properties, was decreased in vaginal and ectocervical tissues (lower tract), increased in endocervix (upper tract) and unchanged in endometrium (upper tract) of postmenopausal women taking MHT. Moreover, estrogen receptor alpha (ERα) and progesterone receptor (PR) expression were also differentially modified by MHT. ERα expression was reduced in the endometrium, endo- and ecto-cervix but increased in the vagina, while PR remained unchanged in vaginal tissue but augmented in the other FRT tissues. These findings suggest that modifications in hormone receptor expression by MHT may have important implications for innate and adaptive immune responses. The extent to which MHT regulates FRT immune function needs to be further examined.

Conclusions

While MHT seems to be associated with improved systemic immune responses, a major gap remains in our knowledge regarding the mucosal immune system in the FRT. Current recommendations indicate the use of hormonal treatment appropriate to relieve menopausal symptoms. The US Food and Drug Administration (FDA) require labeling information to include the following statement: “Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.” Current evidence indicates that different estrogens and progestogens are not recognized in the same way in all cells and tissues. In addition, doses, routes of administration (oral, transdermal, injectable), and the pattern and timing (cyclic versus continuous; interval from menopause to initiation of ET/HT) are all critical determinants of whether a particular woman should receive MHT. In addition, health status during hormone treatment and genetic background are also likely to modulate an individual’s response to ET [64]. Further studies are needed to evaluate if MHT is beneficial to improve immune responses in the FRT and protect postmenopausal women against pathogens of the genitourinary tract.

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Highlights

1. A general failing of the immune system that is gender-specific occurs with aging
2. Immune responses in female reproductive tract are impaired in postmenopausal women
3. Aging women often undergo hormonal therapy relieve menopausal symptoms
4. Some immune parameters are revived upon MHT usage
5. Further studies are required to determine effects of MHT on FRT immune system