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DERLEME/REVIEW

Review on Menopause and Immunity

Menopoz ve İmmunite Üzerine Bir Derleme

Ayşe Nur Çakır Güngör[1], Aslıhan Candevir[2]

[1]Çukurova University Faculty of Medicine, Department of Obstetrics and Gynecology, [2]Department of Infectious Diseases and Clinical Microbiology, Adana, Türkiye

ABSTRACT

Menopausal transition is one of the important life events in a woman's life. Menopausal symptoms are primarily caused by estrogen insufficiency. Estrogen deficiency also causes long-term problems like osteoporosis and an increment of cardiovascular events, and it might have some impact on immunity and vice versa.

In this review we will summarize the effect of menopause and the immune system on each other and elaborate on the relationship between early menopause and the immune system. Finally, we will discuss the impact of menopausal hormone replacement therapy (HRT) on the immune system.

Keywords: Autoimmunity, hormone replacement therapy, immunity, menopause

ÖZET

Menopozal geçiş kadın hayatında önemli bir yaşam olayıdır. Menopozal semptomlar temelde östrojen eksikliğinden kaynaklanır. Östrojen eksikliği uzun dönemde osteoporoz ve kardiyak olaylarda artış gibi problemlere de neden olmaktadır. Östrojen ekiskliğinin aynı zamanda bağışıklık üzerinde de etkileri olabilir. Bağışıklık sisteminin de menopoz üzerinde etkileri olabilir.

Bu derlemede menopozun bağışıklık sistemi, bağışıklık sisteminin de menopoz üzerindeki etkilerini özetleyeceğiz. Erken menopozun immün system üzerindeki etkilerini gözden geçireceğiz. Son olarak da hormon replasman tedavisinin (HRT) bağışıklık sistemi üzerindeki etkilerinden bahsedeceğiz.

Anahtar kelimeler: Otoimmunite, hormon replasman tedavisi, immunite, menopoz

Introductıon

Menopausal transition is one of the important life events in a woman's life. Because of the increased life expectancy menopause will be taken more seriously. Short and long term problems caused by menopause will effect more and more women's life quality.

By menopausal transition women loose functions of their ovaries. So it results in cessation of the fertility and decrement in the hormones produced and secreted by ovaries.

Menopausal symptoms are primarily caused by estrogen decrement. Estrogen deficiency results in vasomotor symptoms, atrophic vaginitis, sleep problems etc. It also causes long-term problems like osteoporosis and an increment of cardiovascular events. Loss of ovarian functions also cause a decrement of testosterone and progesterone. Catastrophic hormonal changes might also have some impact on immunity. Being older also causes some changes in immune system. So to discriminate the effects of age and menopause we will also discuss early menopause. Early menopause will help us to purely understand the effect of menopause.

Autoimmune disease are seen more often in women when compared to males. Perhaps women hormones complicate the pathophysiology.

Immune system and especially autoimmune diseases might have effect on menopause too. Oophoritis, a component of autoimmunity, may cause early menopause.

In this review we will summarize the effect of menopause and the immune system on each other and elaborate on the relationship between early menopause and the immune system. Finally, we will discuss the impact of menopausal hormone replacement therapy (HRT) on the immune system.

A. Menopausal Changes and Immunıty

Estrogen enhances humoral immunity while androgens and progesterone suppress it. Menopausal transition results in deficiency in estrogen, androgens, and progesterone. The immune response during and after this transition is very complex and sometimes controversial.

Menopause has an effect on the innate immune system and decreases the number of white blood cells and all of its components[1]. After menopause, chemotactic cytokines (interleukin-1 [IL-1], IL-6, tumor necrosis factor-alpha [TNF-α]) increase, but the ability to respond to pathogens disrupts[2]. B lymphocyte count and cytotoxic activity of natural killer (NK) cells decrease by menopausal transition[2]. In menopause, increased pro-inflammatory immune status is because of increased NK cells and altered relationships among immunity components[3].

Adaptive immunity changes are also seen in menopause. It is associated with a decline in CD4+ T cell levels, leading to comparatively enhanced immunity following vaccination in aging males relative to females[4]. In the reproductive tract, several changes occur during menopausal transition, like vaginal microbiota changes via endometrial and vaginal atrophy. As in other sites of the body, after menopause, CD4+ T cells decrease in number and percentage in the endometrium[5]. It might be one of the facilitating factors for increased infections of the uterus via vaginal microbial flora after menopause.

In a review published in 2025, authors mentioned an interesting point: menopausal transition changes the gut microbiota, and not only estrogen deficiency but also changed microbiota and immunity have impacts on osteoporosis[6]. The low-grade inflammation caused by the changes in gut microbiota and leaky gut causes increased bone loss via cytokines. Menopausal estrogen deficiency also has a direct effect on cell senescence, which causes alteration of bone remodeling. Cell senescence is also an inflammatory process regulated by receptor activator of nuclear factor kappa-beta ligand (RANKL), TNF-α, and gamma interferon (IFN-γ), which in the end induces immune senescence by pro-inflammatory cytokines like IL-6. This whole cascade leads to chronic inflammation of bone. A study published in 2020 also had similar findings[7]. In a very large sample-sized population-based proteomics study, it was demonstrated that there is a strong relationship among osteoporosis, immunity, and hormonal status[8]. After menopause, the imbalance between pro-inflammatory and anti-inflammatory cytokines leads to some other chronic diseases like diabetes and fatty liver besides osteoporosis[9]. Also, after menopause, the severity of autoimmune diseases such as psoriasis and rheumatoid arthritis (RA) increases[10], This is due to the loss of estrogen's immune-modulating properties. On the contrary, menopause decreases disease progression in systemic lupus erythematosus (SLE)[11].

Vitamin D has some beneficial effects on menopausal problems by altering immunity[12].

A study demonstrated that HIV-positive women have an increased innate immunity by menopausal transition[13]. Since its clinical consequences are not clear, it should be further studied.

B. Early Menopause and Immunıty

Since menopausal transition significantly impacts the immune system, certain symptoms may be attributable to the aging process. Either aging or menopause might cause the changes occurring in immune system. To eliminate the effects of aging early menopause patients can be studied. So early menopause might clarify the effects of hormonal changes of menopause on immunity.

A recent study showed that in Premature Ovarian Failure (POF), there is an increment of T-helper (Th)17. An elevated Th17/T-regulatory (Treg) ratio leads to increased inflammation. The POF group also exhibited elevated levels of IL-17, IL-21, and IL-23[14]. And those alterations reflect the menopausal changes described above. Verma et al[15] showed that patients with POF had higher CD19 levels, which is a B cell marker. A detailed meta-analysis revealed that Plasma Blast-Plasma Cell absolute count and 83 other immune

phenotypes are related to POF[16]. In another study it was demonstrated that pro-inflammatory cytokines increase while anti-inflammatory cytokines decrease in the case of POF[17].

According to a large population-based study, women who underwent oophorectomy had an increased risk of RA (HR 1.21, 95% CI 1.08 to 1.35)[18]. A meta-analysis also demonstrated that menopause is a risk factor for rheumatoid arthritis (RA) (odds ratio: 1.35 [95% CI: 1.04–1.67])[19]. These are also compatible with the menopausal studies. Early menopause has more impact on developing the disease [odds ratio: 2.97 (95% CI: 1.73–4.22)]. This is a demonstrative finding that early menopause has more detrimental effects on immunity.

Wong et al[20] performed an experimental study on rats and found that gene expression of the posterior segment of the eye, which is related to glaucoma, changed in the way of aging rats in ovariectomized rats. Interestingly, in older ages, ovariectomy had little effect on that kind of gene expression pattern, which means early menopause can cause inflammation in the posterior eye segment that can make us speculate that early menopause can cause inflammation all over the body and cause changes like an aging body.

On the other hand, an interesting review concludes that herbal medicine used in the treatment of POF has beneficial effects through immunological pathways. They regulate molecules of immunity, ILs, TNF-α, INF-γ, vascular endothelial growth factor (VEGF), TGF-β, etc[21].

C. Autoımmunıty and Menopause

Approximately one-third of patients with POF have an autoimmune disease. While autoimmune antibodies cause oophoritis and cause POF in some patients, autoimmune disease accompanies some other POF cases. Either before or after POF diagnosis, patients tend to be diagnosed with various autoimmune diseases. Dai et al[22] defined an animal model that causes POF in offspring by triggering maternal autoimmunity.

Poor ovarian reserve (POR) is one of the early signs of POF. Huang et al[23] conducted a study on in vitro fertilization (IVF) patients with and without POR and with and without anti-ovarian antibodies (AOA). They demonstrated that AOA is more prevalent in POR patients. They also showed that peripheral blood CD56+ NK cell levels, NK cytotoxicity, CD19 +CD5 + B-1 cell levels, and IFN-γ/IL-10-producing Th1/Th2 cell ratios were significantly higher in POR patients. TNF-α/IL-10-producing Th1/Th2 cell ratio was significantly higher in patients who had both POR and AOA. Homocysteine and vitamin D levels were significantly lower in patients with POR and AOA. Plasminogen activator inhibitor-1 (PAI-1) level was significantly higher in patients with POR and AOA. In the POR and AOA group, the prevalence of anti-phospholipid antibodies was also significantly higher.

Sun et al[24] measured the IL-6 and IL-21 levels in POF patients with autoimmune diseases like Hashimoto thyroiditis, RA, ulcerative colitis, Crohn's disease, and SLE. He found that IL-6 and IL-21 levels were negatively correlated with estradiol (E2) levels. SLE increases prolactin, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) in women[25]. A cohort study demonstrated that women with inflammatory bowel disease significantly have earlier menopausal transition[26].

In various studies, vitamin D treats the consequences of POF via inhibiting neutrophil extracellular traps[27]. There is a rapidly growing literature on stem cell and POF treatment[28]. In an animal model, umbilical cord-derived CD146+/− mesenchymal stem cells improved the hormone profile of POF mice[29]. A rat study also showed improvement by umbilical cord stem cells[30]. In the mice model of POF and umbilical cord stem cell therapy, it was shown that it was working through regulating Treg cells by IFN-γ and tissue growth factor (TGF)-beta[31]. Another rat study showed that CD146+ menstrual blood stem cells cause ovarian rejuvenation and heal some hormonal parameters like FSH and E2[32]. In the future, stem cell-based therapies might dominate the POF treatments.

D. Hormone Replacement Therapy (HRT) and Immunıty

As the huge literature shows a strong link between menopause and immunity and also autoimmunity, one can be curious about the potential effects of HRT on immunity. Potentially, HRT might reverse the effects of menopause on immunity. Literature has some clinical and experimental studies on the subject.

It is shown that HRT reverses the CD4/CD8 ratio and decreases the inflammation of menopause[33]. Surgical menopause causes an increment of CD8+ T cells and a decrement of B cells, the CD4+/CD8+ ratio, IL-4 levels, and IFN-γ, and HRT reverses those changes[34].

In an experimental study it was demonstrated that estradiol replacement therapy also improves innate immunity[35]. While oral estrogen increases monocytes, leading to a better immune response, transdermal estrogen increases both monocytes and Th cells. So transdermal replacement might be a better choice for menopause[36]. Postmenopausal women using HRT exhibited elevated Langerhans cells, inflammatory dendritic cells, and macrophage counts in the dermis[37].

On the contrary, a cohort study showed that HRT use (HR 1.46, 95% CI 1.35 to 1.57) and HRT duration (HR 1.02, 95% CI 1.01 to 1.03) were also associated with a higher risk of RA[18]. The progesterone component of HRT is omitted mostly. Whereas postmenopausal progestogen usage is shown to decrease RA risk (HR ¼ 0.77; 95% CI 0.6, 0.9)[38]. The majority of the literature concludes that HRT usage in SLE patients might cause flare-ups of symptoms of SLE[39].

There is a lack of consensus among studies regarding the impact of HRT on immunity. Interestingly, postmenopausal E2 therapy did not result in any changes to either humoral or cellular immunity markers[40].

Conclusıon

There is a huge and expanding literature on menopause and immunity. An extensive body of literature generates additional inquiries regarding that literature. Mechanisms of altered immunity caused by decreased ovarian functions and effects of HRT, particularly progesterone, must be clarified with further studies. Stem cell therapies for POF can be investigated by clinical research. Autoimmune disease and inflammation might be causing more damage to ovaries than we have anticipated and may be investigated further. Microbiota and the upper reproductive tract are also other areas of potential interest.

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Correspondence Address / Yazışma Adresi
Ayşe Nur Çakır Güngör
Çukurova University Faculty of Medicine
Department of Obstetrics and Gynecology
Adana, Türkiye
e- mail: dr_aysecakir@hotmail.com

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