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REVIEW ARTICLE

Vitamin D and the Immune System in Menopause: A Review

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Menopause is a normal phenomenon in a woman's life cycle involving multiple health-related issues that contribute to physical instability. Changes in the immune system in postmenopausal women are caused by estrogen deprivation along with age. Increased proinflammatory serum marker levels, cytokine responses in body cells, decreased CD4 T and B lymphocyte levels, and natural killer cell cytotoxic activity are also observed during postmenopause. Moreover, vitamin D, in addition to its classical effects on calcium homeostasis and bone density, plays an important role. Current evidence indicates that vitamin D regulates innate and adaptive immune responses; however, vitamin D deficiency is linked to increased autoimmune activity and infection susceptibility. This review provides an overview of the consequences of immune alterations as an outcome of aging in postmenopausal women and the benefit of vitamin D supplementation.

Key Words: Immune system, Menopause, Vitamin D

INTRODUCTION

The stages of a woman's life are based on their reproductive cycle, which start with menstruation and end with the menopausal period. Aging is a natural phenomenon that affects all humans and is associated with decreased overall body function. In women, menopause is also associated with aging in women. During menopausal transition and post-menopause, there is a higher risk of various age-related diseases and health complaints [1]. For this reason, researchers have attempted to identify effective remedies that can promote immunity in women during menopause.

Vitamin D is a steroidal hormone that participates in calcium metabolism and bone homeostasis. Recently, interesting new aspects of vitamin D metabolism have been characterized, and over the past few decades, several additional skeletal effects have been attributed to vitamin D function. We summarize these beneficial effects by focusing on the immune system in menopausal and post-menopausal women (Fig. 1).

IMPACT OF AGING ON THE IMMUNE SYSTEM

The immune system is influenced by age-related changes that occur in the endocrine, nervous, digestive, cardiovascular, and skeletal muscle systems. The age-related decline of the immune system results in

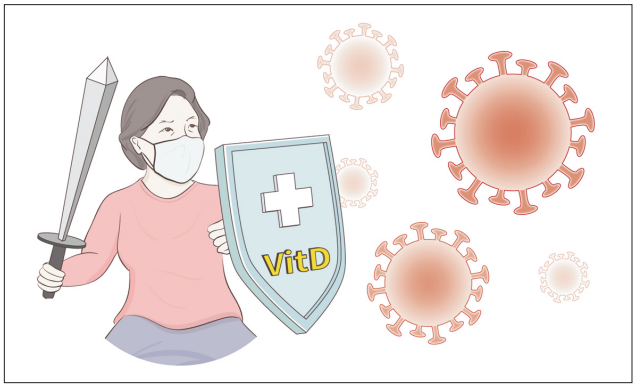

Fig. 1. Menopausal women against antigens with vitamin D.

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increased susceptibility to infectious diseases, lower vaccination responses, increased autoimmunity, and chronic disease, including the prevalence of cancer [2]. Changes in the immune system due to aging are commonly referred to as immunosenescence and are associated with a decrease in response to pathogens and increased rates of morbidity and mortality in the elderly (Table 1) [3,4]. A reverse CD4/CD8 ratio, increased number of differentiated terminal T lymphocytes, naïve T lymphocyte loss, oligoclonal expansion of virus-specific T lymphocytes, and alteration of natural killer (NK) cells are distinctive signs of immunosenescence [5,6]. Hence, aging leads to changes in innate and adaptive immune functions.

The innate immune system is the first line of defense against invasive pathogens. Their role is to trigger an inflammatory reaction, phagocytose and kill pathogens, recruit NK cells, and promote the maturation and migration of dendritic cells that initiate an adaptive immune response [7]. The innate immune system consists of a cell network of neutrophils, NK cells, NK T cells, monocytes, macrophages, and dendritic cells mediated by mechanisms such as chemotaxis, phagocytosis, natural cytotoxicity, cellular interactions, and soluble mediators or cytokines. The number of NK cells increases with age, which plays an important role in protecting against viral pathogens and tumors. However, there is a decrease in cytotoxicity and cytokine production capacity during the remodeling of the different NK cells subsets [8].

Chemotaxis is dysregulated in neutrophils, monocytes/macrophages, and dendritic cells during aging. And macrophages and dendritic cells have the ability to phagocytose pathogens, which decreases with aging in addition to the reduced production of superoxides by neutrophils and monocytes/macrophages [9]. Moreover, dendritic cells begin to lose their ability to present antigens and are less capable of stimulating T- and B cells [10]. In addition, recent studies have shown that the function of Toll-like receptors, which are one of the main families of receptors for innate, is dysregulated during aging [11,12].

The adaptive immune system is also downregulated during aging. It is associated with decreased production of naïve T cells and increased production of senescent, inflationary, or depleted T cells that are functionally inactive or dormant [13]. Persistent viral infections, such as influenza virus, cytomegalovirus, and varicella zoster virus, have been consistently detected in seniors and are regarded as biomarkers of immunosenescence [14]. The function of B cells is also reduced in older people and their ability to produce potent and high-affinity antibodies decrease, in addition to a loss of their diverse repertoire. Age-related immune deficits lead to infection susceptibility and off-target vaccine responses, which contributes to the higher risk of infection in the elderly and creates a need to optimize treatments and vaccines specifically for aging populations [15].

Table 1. Summary of the changes in imuune system with aging

Immunity	Cell	Aging-associated changes
Innate	Monocytes/ macrophages	Phagocytic activity ↓ MHC II expression ↓ ROS and cytokine production ↓
	Dendritic cells	Maturation and antigen presentation ↓ Altered TLR expression and signals Altered CD80 and CD86 expression Impared antigen uptake
	Neutrophils	Chemotaxis ↓ MHC II expression ↓ ROS and cytokine production ↓ Altered TLR expression and signals
Adaptive	T cells	Naïve T cells ↓ T cell response to new antigen ↓ Numbers of senescent T cells and exhausted T cells ↑
	B cells	Naïve and circulating B cells ↓ Antigen specific antibody production ↓ Altered memory B cell homeostasis Limited diversity in BCR repertoire

MHC: major histocompatibility complex, ROS: reactive oxygen species, TLR: Toll-like receptor, BCR: B cell receptor.

POST-MENOPAUSAL CHANGES IN THE IMMUNE SYSTEM

Women have higher risk of developing autoimmune diseases, indicating that certain diseases are mediated by sex hormones [1]. Numerous studies have reported a gender-based decline in immune function due to the multiple immune parameters that respond to estrogen; a number of pathophysiological conditions are modified by the natural changes in estrogen levels in post-menopausal women. Indeed, increase in pro-inflammatory serum marker (interleukin 1 [IL-1], interleukin 6 [IL-6], and tumor necrosis factor alpha [TNF-α]) levels and body cell response to these cytokines and decrease in CD4 T and B lymphocyte levels and cytotoxic activity of NK cells were reported in post-menopausal

women [1,16].

Inflammatory conditions are affected by the immune microenvironment in post-menopausal women due to the lack estrogen, which acts as an enhancer of humoral immunity, while androgens and progesterone function as natural immunosuppressants. Post-menopausal women have higher chronic levels of the pro-inflammatory cytokines monocyte chemotactic protein 1 (MCP-1), TNF-α, IL-1, and IL-6, as well as decreased ability to respond to pathogens or stimuli [16,17]. Decreased CD4 T and B lymphocyte counts and reduced cytotoxic activity of NK cells were also observed [16].

IL-6 is a key component of bone reabsorption through the activation of osteoclasts and might be correlated with other diseases, such as arteriosclerosis, diabetes, and cardiovascular disease [1]. In the patient group with these underlying diseases, the immune response decreased and the sensitivity to pathogenic invasion and infection increased when compared with healthy people.

The short-term effects of surgical menopause and estrogen replacement therapy (ERT) on the immunity profile were examined using blood serum immune markers from perimenopausal women who underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH + BSO) for uterine fibroids [18]. One month after surgery, CD8 T cell number increased, whereas B cell, CD4/CD8 T cell ratio, and serum IL-4 and interferon gamma (IFN-γ) levels decreased; however, menopausal hormone therapy (MHT) reversed these effects [18]. In another study, women with premature ovarian insufficiency (POI) had decreased CD3+ lymphocyte levels compared with pre-menopausal women, whereas CD19+, CD3+8+, and CD8+57+, and a large percentage of CD5+ lymphocytes were observed in the CD19+ cell population [19]. These immune changes indicated that estrogen plays a significant role in the function of the female immune system.

INFECTION SUSCEPTIBILITY AND VACCINE RESPONSES AMONG POST-MENOPAUSAL WOMEN

A couple of studies have described increased infection susceptibility in post-menopausal women. A second peak of human papillomavirus (HPV) infection was reported among post-menopausal women [20,21], and it is believed that new HPV infections among older women are attributable to reduced immune responses. There is also an increase in human immunodeficiency virus (HIV)-1 infection among post-menopausal women, primarily through heterosexual transmission [22,23]. Estrogen deficiency associated with menopause and normal thymic tissue reduction associated with aging can affect CD4 cell recovery and HIV replication [24]. A European study that compared serodiscordant couples found that women older than 45 years of age were four times more likely to contract HIV than women younger than 45 years [25]. Moreover, elderly women have higher mortality rate from HIV than men (32% in women, 18% in men) [26]. Cell-based studies have shown an increase in the number of HIV co-receptors and elevated cervical CCR5 expression in post-menopausal women compared with those in pre-menopausal women, although further studies are needed to determine the relationship between elevated CCR5 expression and increased HIV-1 susceptibility [27]. Another study reported enhanced HIV transcription in the ectocervical mucosal surface in post-menopausal women than in pre-menopausal women, which was associated with the increased secretion of pro-inflammatory cytokines such as IL-1β, IL-6, MCP-1, growth-regulated oncogene-α, and IFN-γ–inducible protein-10 expression [28,29]. Aging has also been linked to the reduced efficacy and effectiveness of vaccines [30]. The immune response in elderly people to vaccines is often lower than that in younger adults. Age-related changes in antigen uptake, processing, and labeling, as well as functional defects in T cells also reduce antibody responses [31]. In addition, antibody production analysis showed that inflammation can also contribute to reduced vaccine responses due to endogenous cell defects [31,32].

Urinary tract infections are the most common bacterial infection in post-menopausal women. Maintenance of a low vaginal pH by the production of lactobacilli and lactic acid could play an important role in the prevention of bacteriuria [33]. In some studies, vaginal estrogen administration appeared to be effective in preventing recurrent urinary tract infections with lactobacilli species recovery [34-36].

EFFECT OF VITAMIN D ON THE IMMUNE SYSTEM

The main physiological function of vitamin D is its role in bone homeostasis [37]. However, current studies clearly support an interaction between vitamin D and

immune system cells beyond its regulation of calcium metabolism [38,39]. The vitamin D receptor (VDR) and 1α-hydroxylase (CYP27B1) are widely expressed in immune cells, including T cells, B cells, dendritic cells, macrophages, and monocytes, which are necessary for the conversion of 25-hydroxyvitamin D to its active form. Vitamin D and VDR signaling together play an inhibitory role against autoimmune and anti-inflammatory effects, promoting dendritic and regulatory T cell differentiation, reducing T helper Th17 cell responses and inflammatory cytokine secretion [40-42]. This suggests that vitamin D can modulate innate and adaptive immune responses [43-45]. Vitamin D has also recently been shown to produce antibacterial peptides and stimulate the autophagy activity of macrophages, promoting an antibacterial response [43]. Furthermore, epidemiological evidence indicates an important link between vitamin D deficiency and VDR genetic polymorphisms and the severity of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, type 1 diabetes, and inflammatory bowel diseases [46-49]. As a result, considerable effort has been made to explore the potential therapeutic benefits of vitamin D supplementation in autoimmune diseases [46-52].

POSSIBLE ANTIVIRAL ACTION OF VITAMIN D

Previous studies have found that vitamin D deficiency predisposes patients to respiratory tract infections, indicating vitamin D has a functional role in respiratory infections [53,54]. However, the potential interactions between viral infection and vitamin D appear to be more complex than previously thought [55]. Some observational studies have shown lower levels of vitamin D among HIV-positive people, and vitamin D supplements seemed to reverse some changes in the immune system in HIV-positive patients [56,57]. Another study has shown that vitamin D induction by antimicrobial peptides may have antiviral effects [58]. In vitro reports have hypothesized that respiratory viruses regulate the expression of vitamin D receptors in human bronchial epithelial cells and that this regulation affects the antiviral response to exogenous vitamin D [59]. Despite decreased levels of vitamin D receptors in rhinovirus-infected epithelial cells, exogenous vitamin D could increase antiviral defense against cathelicidin and innate interferons [60].

CONCLUSION

We have presented several factors and changes that affect women during menopausal transition and suggested how these factors affect the immune system. Several studies have reported a link between vitamin D and immunity; however, as the etiology of menopausal immunity is multifactorial, the regulation of immunity is a part of aging. Although complementary treatments with cholecalciferol have been shown to have beneficial effects on the immune system in post-menopausal women, large multicenter studies are needed to investigate the effects of supplemental vitamin D therapy on the long-term clinical outcomes in post-menopausal women.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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