

Impact of Vitamin E on Immune Function and Infectious Diseases in the Aged

Sung Nim HAN, Ph.D., R.D and Simin Nikbin MEYDANI, DVM, Ph.D.
JM USDA Human Nutrition Research Center on Aging at Tufts University
Friedman School of Nutrition Science and Policy at Tufts University

Vitamin E is a potent peroxy radical scavenger that can prevent the propagation of free radical damage in biological membranes. Evidence suggests beneficial effects of supplemental vitamin E on immune functions, especially in the aged. This presentation will focus on the role of vitamin E in modulating immune responses and mechanisms by which vitamin E exerts its effects. Findings from infectious disease models and gene expression studies will be discussed.

Age-associated dysregulation of immune function has been clearly demonstrated. Immunological changes observed with aging include decreased lymphocyte proliferation, delayed type hypersensitivity (DTH) response, and interleukin (IL)-2 production; a shift toward T helper (Th) 2 response; an increase in T cells expressing memory phenotype; a decrease in antibody response to vaccination; and an increase in the production of suppressive factors such as prostaglandin (PG) E₂.

Vitamin E supplementation has been shown to have an immunostimulatory effect in aged animals and elderly humans. An earlier study (1) in 32 healthy elderly men and women aged >60 years supplemented with either placebo or 800 mg *dl*- α -tocopherol for 30 days showed that vitamin E supplementation was associated with increased DTH response, proliferative response to ConA, and IL-2 production. Decreased PHA-stimulated PGE₂ production by peripheral blood mononuclear cells and decreased plasma lipid peroxide concentration was observed with vitamin E supplementation as well.

Whether this immunostimulatory effect of vitamin E was associated with an increased resistance to infectious diseases was investigated using influenza infection model. Vitamin E supplementation (500 mg/kg diet for 8 weeks) in old mice resulted in significantly lower influenza viral titer (2). IL-2 and IFN- γ production (Th1 response) by splenocytes increased significantly after influenza infection in

vitamin E-supplemented old mice, whereas old mice fed the control diet (30 mg vitamin E/kg diet) were unable to induce efficient Th1 response. A significant inverse correlation between viral titer and IFN- γ production was observed indicating that a higher IFN- γ production was associated with a lower viral titer. Dysregulation of Th1 and Th2 functions are observed with aging and these changes in Th1/Th2 balance can contribute to the delayed clearance and recovery from influenza infection as Th1 clones are cytolytic *in vitro* and protective against lethal challenges *in vivo*, whereas Th2 clones are noncytolytic and not protective (3, 4). Therefore, the protective effect of vitamin E against influenza infection appears to be mediated through reducing the viral load partly by enhancing Th1 response. Vitamin E also reduced the bacterial count in the lungs of the mice pre-exposed to influenza virus, abolishing the priming effect of influenza infection on *Staphylococcus aureus* (5).

Clinical significance of vitamin E supplementation in regards to protection against infectious diseases in humans has been investigated in a randomized, double blind study (6). 617 people aged over 65 residing at 33 nursing homes in the Boston area received either a placebo or 200 IU of vitamin E daily for one year. The results of this clinical trial showed that significantly fewer vitamin E-supplemented subjects acquired one or more respiratory infections or upper respiratory infections. However, supplementation with vitamin E had no significant effect on incidence or number of subjects acquiring lower respiratory infections. Vitamin E group had a lower incidence of common colds and fewer subjects in the vitamin E group acquired one or more common colds. In conclusion, the results of this clinical trial show that vitamin E supplementation significantly reduces the risk for acquiring respiratory infections in the elderly.

In order to determine the mechanisms by which vitamin E exerts its immunostimulatory effect, we compared the gene expression profiles of T cells from old or young mice fed a control or a vitamin E-supplemented diet (7). Vitamin E showed a significant impact on gene expression profiles of T cells

in few different categories of genes, including those involved in cell cycle and Th1/Th2 balance.

Vitamin E increased expression of cyclin B2, Cdc2, and Cdc6 in old T cells, which might contribute to the increased ability of T cells from the old mice to progress through cell division and proliferate.

Vitamin E also had a significant impact on expression of genes involved with a Th1/Th2 balance.

Vitamin E increased gene expressions of IL-2 and IL-1 receptor antagonist, and decreased the expression of IL-4, a major Th2 cytokine and stimulator of Th2 response. IL-1 receptor antagonist was reported to play a role in up-regulation of Th1 response (8).

In conclusion, studies have demonstrated an improvement in immune response in animals and humans supplemented with more than the recommended level of vitamin E. This enhancement of immune response is associated with increased resistance to infectious diseases in animal models. Results from a recent clinical trial indicate that vitamin E supplementation reduces the risk of acquiring upper respiratory infections in elderly subjects. This immunoregulatory effect of vitamin E is mediated indirectly by a reduced production of suppressive factors such as PGE₂ by macrophages and directly by an increase in cell division capacity and IL-2 production by naïve T cells and by the changes in expression of genes related to cell cycle and Th1/Th2 balance of T cells.

References

1. Meydani SN, Barklund MP, Liu S, et al. Vitamin E supplementation enhances cell-mediated immunity in healthy elderly subjects. *Am J Clin Nutr* 1990;52:557-563.
2. Han SN, Wu D, Ha WK, et al. Vitamin E supplementation increases T helper 1 cytokine production of old mice infected with influenza virus. *Immunology* 2000;100:487-493.

3. Graham MB, Braciale VL, Braciale TJ. Influenza virus-specific CD4+ T helper type 2 T lymphocytes do not promote recovery from experimental virus infection. *J Exp Med* 1994;180:1273-1282.
4. Moran TM, Isobe H, Fernandez-Sesma A, Schulman JL. Interleukin-4 causes delayed virus clearance in influenza virus-infected mice. *J Virol* 1996;70:5230-5235.
5. Gay R, Han SN, Marko M, Belisle S, Bronson R, Meydani SN. The effect of vitamin e on secondary bacterial infection after influenza infection in young and old mice. *Ann N Y Acad Sci* 2004;1031:418-21.
6. Meydani SN, Leka LS, Fine BC, et al. Vitamin E and respiratory tract infections in elderly nursing home residents: a randomized controlled trial. *JAMA* 2004;292:828-36.
7. Han SN, Adolfsson O, Lee CK, Prolla TA, Ordovas J, Meydani SN. Vitamin E and gene expression in immune cells. *Ann N Y Acad Sci* 2004;1031:96-101.
8. Lin KW, Chen SC, Chang FH, Kung JT, Hsu BR, Lin RH. The roles of interleukin-1 and interleukin-1 receptor antagonist in antigen-specific immune responses. *J Biomed Sci* 2002;9:26-33.