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Vitamin D and sepsis

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ABSTRACT

Vitamin D receptors are located in body tissues and cells. In various physiological processes of the body the primary circulating form of vitamin D, 25-hydroxyvitamin D, will become the active form, 1,25-dihydroxyvitamin D, through many enzymatic. Although different functions of vitamin D has been identified, reducing the possibility of several chronic diseases, including common cancers, autoimmune, infectious, and cardiovascular diseases is proposed as the major role of this component. According to various experimental and clinical studies, vitamin D affects the immune system activity. In this review we study the possible effects of vitamin D on sepsis. The purpose of this review is to evaluate and summarize the role of vitamin D in the immune system, with particular focus on infections and sepsis. We studied different areas related to vitamin D in the literature review including its roles sepsis and infection incidence, as well as seasonal and racial variation in sepsis. Based on evidence, vitamin D positively affects the immune system, so it might act as a therapeutic strategy. Despite several experimental studies which demonstrated the beneficial effects of vitamin D on improved functioning of the immune system, its association with prevention or management of infections and sepsis is not revealed through clinical investigations.

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Introduction

Vitamin D roles in the optimal functioning of organ systems are going to become an attractable field for scientists around the world. Although its roles in bone health and calcium homeostasis are mostly well defined, presumed vitamin D influences in other body systems are yet to be defined. Discovering vitamin D receptors and 25-hydroxyvitamin D-1α-hydroxylase (1α-OHase) in many extraskeletal tissues and also finding vitamin D response element (VDRE) in over 900 genes are the reasons which upraised global

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attention to this steroid hormone (1). From the clinical and epidemiological points of view, it is suggested that risk of systemic infection, cardiovascular disease, lung disease and diabetes are decreased through maintain optimal vitamin D status (2-6).

Vitamin D and the Immune System

By detecting vitamin D receptors (VDR) in activated $CD4^+$ and $CD8^+$ T cells, B cells, neutrophils, macrophages and dendritic cells (7), a wide variety of roles in immune systems linked to vitamin D. It has been shown that vitamin D has an inhibitory effect on antibody response to pneumococcal antigens in mice (8) and also causes B and T cells proliferation and differentiation (9). On the other hand, some studies try to uncover vitamin D roles in the innate immune system. Anti-pathogen and barrier function of neutrophils and monocytes against invading organisms are among its functions as well as identification of pathogens through highly conserved pathogen-associated molecular patterns (PAMP) (7,10).

Vitamin D and Local Immune Defense

Beside systemic inflammatory response, vitamin D has been found important in initiation of local responses to pathogens. It is proven that vitamin D3 could markedly stop growth and even kill various strains including Staphylococcus aureus, Streptococcus pyogenes, Klebsiella pneumoniae, and Escherichia coli in-vitro (11). Additionally, it is shown that treating respiratory syncytial virus infected cells by $1,25(OH)_2D$ could diminish inflammatory proteins without changing the viral load (12). In support of vitamin D role in local immune defense, Nelson et al. showed that 1a-OHase is up-regulated in infiltrating macrophages in infected tissues of bovine model and provide $1,25(OH)_2D$ which affect local immune reactions against pathogens (13).

Clinical Research on Vitamin D and Infection

In clinical studies, relationship between vitamin D serum levels and respiratory infections is an attractive field. In a study of National Health and Nutrition Examination Survey (NHANES), Ginde et al. evaluated serum 25(OH)D levels in about 18000 volunteers who participated in this study. It was observed that serum 25(OH)D levels conversely related to upper respiratory tract infections (URTI) (14).

Although Sabetta et al. showed that 38 ng/mL or greater levels of serum 25(OH) D is accompanied with a 100% decline of URTI incidences (15), Laaksi et al. couldn't find a significant relationship between the days absent from work due to URTI and daily 400 IU vitamin D3 supplementation (16). However it should be considered that in Laaksi et al. study, only 30% of volunteers receiving daily supplementation had a >32 ng/mL 25(OH)D serum level in the end of study. Also in Li-ng et al. study, no prevention benefits observed when 162 adults received 2000 IU vitamin D3 for 12 weeks in winter season in regards of incidence or severity of URTI (17). Some observational and interventional studies evaluate the relationships and effects of vitamin D regarding to acute lower respiratory tract infections (ALRTI). Some case-control studies revealed controversial results about relationship between vitamin D level and ALRTI in children. Although in three studies it was observed that hospital admission due to ALRTI is associated with lower vitamin D serum levels (18-20), in another two studies it is claimed that there is no significant association between ward or ICU hospitalization due to ALRTI and vitamin D status (21,22). In two separated interventional studies, hopeful results obtained about suppressive effect of vitamin D supplementation in incidence of ALRTI (23) and influenza A

(24) infection in children. These studies with controversial results indicate that vitamin D effect on prevention of infections including respiratory infections is too small and larger sample size is needed to clarify possible roles of this vitamin. It should be remember that respiratory infections are the leading cause of sepsis in US which indirectly demonstrate the Vitamin D could partly prevent sepsis at least by declining respiratory infections incidences (25).

Vitamin D and the Seasonal Variation in Sepsis

In a large prospective study in USA between 1979 and 2003, a seasonal variation observed about sepsis incidence in national hospitals setting. In this way, the heaviest load of patients with sepsis and severe sepsis was related to winter, though the least patients administered to hospitals with sepsis related to fall. This difference was statistically significant and it was more prominent in Northeast USA (26). The same seasonal pattern was seen in patients with respiratory infections, as the most prevalent cause of sepsis (26).

Serum 25(OH)D levels varied annually as well, which is in the highest level in fall and its lowest serum level could be seen at the end of winter (27). This variation could be explained by variation of solar zenith angle in different seasons and subsequent variation of the amount of ultraviolet-B (UVB) radiation which is necessary in order to vitamin D is produced through the skin (28). Variation in amount of UVB is more prominent in the regions farther to equator. It seems that this hypothesis could relate parallel seasonal variation of vitamin D to respiratory infections and sepsis. However it should be remind that there are numerous defined and undefined factors which could play role in vitamin D synthesis (28,29).

Conclusion

Various roles of vitamin D in different body systems and especially immune system raise attentions to this hypothesis that vitamin D is a key component in defending against invading pathogens. Both basic science and clinical studies emphasize on immunomodulatory functions of vitamin D in preventing infections including respiratory infections which are the leading cause of sepsis. No study is available right now which demonstrate an obvious relationship between sepsis incidence and severity and vitamin D serum levels. Parallel seasonal patterns of sepsis and vitamin D serum levels and also the results of some observational and interventional studies could be enough reasons in order to conduct studies to uncover possible relationships between vitamin D and sepsis. If any relationships found, vitamin D supplementation could be an effective and safe way in order to decrease economical and social burden of sepsis as well as promoting hygiene level of society.

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Conflict of Interest

The authors declare no conflict of interest.

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