**Vitamin D: Is There a New Era?**

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**ABSTRACT**

**Background:** In recent decades, much interest has been focused on investigating new roles of vitamin D in human body beyond the mineral-ion homeostasis. **Methods:** By searching medical databases such as PubMed, over 16000 articles were found which have been published since 2000 on novel aspects of vitamin D in health and diseases. **Results:** Of great interest was the effects of vitamin D on decreasing the risk of several chronic illnesses, including common cancers, autoimmune, infectious, and cardiovascular diseases. In this review, the new roles of vitamin D that have recently been investigated were addressed. **Conclusions:** Due to the vast prevalence of vitamin D deficiency worldwide, it seems that time has come to conduct well-designed clinical trials and meta-analysis to explore the effectiveness of vitamin D supplementation in treatment of common diseases. Finally, the progression in cellular and molecular methods and technology will shed new lights on vitamin D roles in health and disease.

**Keywords:** Vitamin D; Antioxidant; Inflammation; Gastrointestinal diseases; Depression

Vitamin D and chronic inflammation

Recently, non-calcemic functions of vitamin D, especially anti-inflammatory and immunomodulatory effects have attracted much attention. The beneficial effect of vitamin D intake on high-sensitive C-reactive protein (hs-CRP) was investigated in patients with non-alcoholic fatty liver disease (NAFLD) (Figure 1) (Sharifi et al., 2014). It has been found that 1,25(OH)2D inhibits the T-helper1 response and may promote T-helper2 response, in other words, it could reduce production of inflammatory cytokines and induce anti-inflammatory response (Cantorna et al., 2004).
Antioxidant effects of vitamin D

The antioxidant role of vitamin D was initially proposed by Wiseman in 1993; it was sown that vitamin D₃ and its active form 1,25(OH)₂D₃ inhibited iron dependent liposomal lipid peroxidation (Wiseman, 1993). The structural similarity of vitamin D compounds to cholesterol and ergosterol suggested for their membrane antioxidant ability (Wiseman, 1993). For the first time, it was found that improving vitamin D status in NAFLD patients could effectively reduce serum levels of Malondialdehyde (MDA) (Figure 2) (Sharifi et al., 2014).

It was reported in recent clinical studies on pregnant women that vitamin D supplementation could increase the serum total antioxidant capacity and glutathione levels (Asemi et al., 2013). However, no association was found between 25(OH)D levels and activities of serum antioxidant enzymes in the study that assessed the relation between serum vitamin D levels and body antioxidant status in ischemic stroke patients (Afshari et al., 2015).

Vitamin D and gastrointestinal diseases

Cumulative evidence has implicated the roles of vitamin D deficiency in increasing susceptibility to various gastrointestinal (GI) disorders, including colorectal disease, inflammatory bowel diseases (IBD), and irritable bowel syndrome (IBS)
A high risk of IBD has been associated with deficient or insufficient levels of vitamin D, unhealthy lifestyle, as well as presence of vitamin D related genetic polymorphisms (Basson, 2014). IBS is also a functional GI disorder. In this regard, it was demonstrated for the first time that supplementation with 50,000 IU vitamin D3 every 14 days for 6 months improves the quality of life and clinical symptoms of patients with IBS (Abbasnezhad et al., 2016).

Vitamin D and depression
Vitamin D modulates the hypothalamic-pituitary-adrenal axis, regulating adrenalin, noradrenaline, and dopamine production through vitamin D receptors (VDRs) in the adrenal cortex and protects against the depletion of dopamine and serotonin centrally (Spedding, 2014). Therefore, a biological plausibility has been established for vitamin D effect on depression. Efficacy of vitamin D supplements in depression is controversial, awaiting further literature analysis. Premenstrual syndrome (PMS) is a condition with episodes of physical and psychological signs (Freeman, 2003). Based on the possible roles mentioned above, it seems that vitamin D status is associated with PMS severity. However, there are a limited number of studies assessing the association of vitamin D with this condition. Thus, a cross-sectional study was designed to compare the nutritional status of vitamin D in young students affected by PMS with those of normal participants. The results, however, showed no significant differences in serum levels of vitamin D between the two groups (Saeedian Kia et al., 2015). Further studies will reveal more facts in this area.

Conclusions
In summary, vitamin D may exert important roles in prevention and treatment of many chronic diseases. As a result, it is necessary to maintain the sufficient serum levels of vitamin D among community members through food fortification and supplementation.

Due to the vast prevalence of vitamin D deficiency worldwide, it seems that time has come to conduct well-designed clinical trials and meta-analysis to explore the effectiveness of vitamin D supplementation in treatment of common diseases.

Finally, the progression in cellular and molecular methods and technology will shed new lights on vitamin D roles in health and disease.

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