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Review Article

The Immunostimulatory Properties of Vitamin D

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Abstract

Vitamin D has been associated with the regulation of bone metabolism. However, increasing evidence demonstrates a strong association between vitamin D signaling and many biological processes to that immunostimulatory and immunomodulatory effects on the immune system. the presence of the vitamin D receptor in multiple immune cells, such as monocytes, dendritic cells, and activated T cells, vitamin D with a novel role in modulating immunological functions and its subsequent role in the development or prevention of autoimmune diseases such as systemic lupus Erythematosus, Type-1 Diabetes mellitus and multiple sclerosis. In the present review, the multiple and diverse effects of vitamin D on the immune system are reviewed.

Keywords: Vitamin D, Immune system, Immunomodulation, Vitamin D receptor (VDR), Vitamin D receptor (VDR).

INTRODUCTION

The name vitamin D covers a group of liposoluble steroid compounds of different origins with similar chemical structures and the same biological effects. Two main forms of vitamin D are ergocalciferol (vitamin D 2) and cholecalciferol (vitamin D 3) (Figure 1).

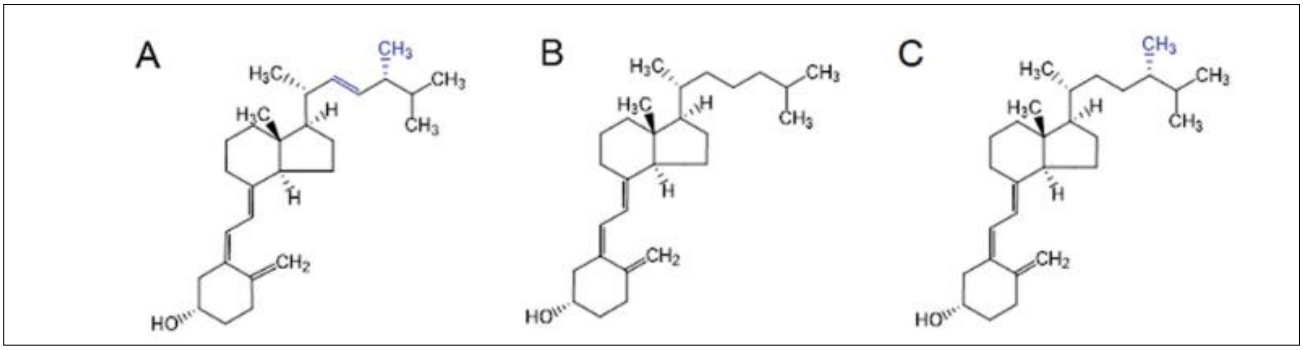

Figure 1: Chemical structure of vitamin D2 (A), vitamin D3 (B), and vitamin D4 (C). In online version, differences are shown in blue

Vitamin D 1 is a historical term for a mixture of vitamin D2 with lumisterol. Vitamin D 2 is Synthesized by the irradiation of ergosterol in yeast, while vitamin D 3 is generated from 7-dehydrocholesterol after ultraviolet (UV)-B irradiation in the human skin this being a unique property among vitamins (Figure 2).

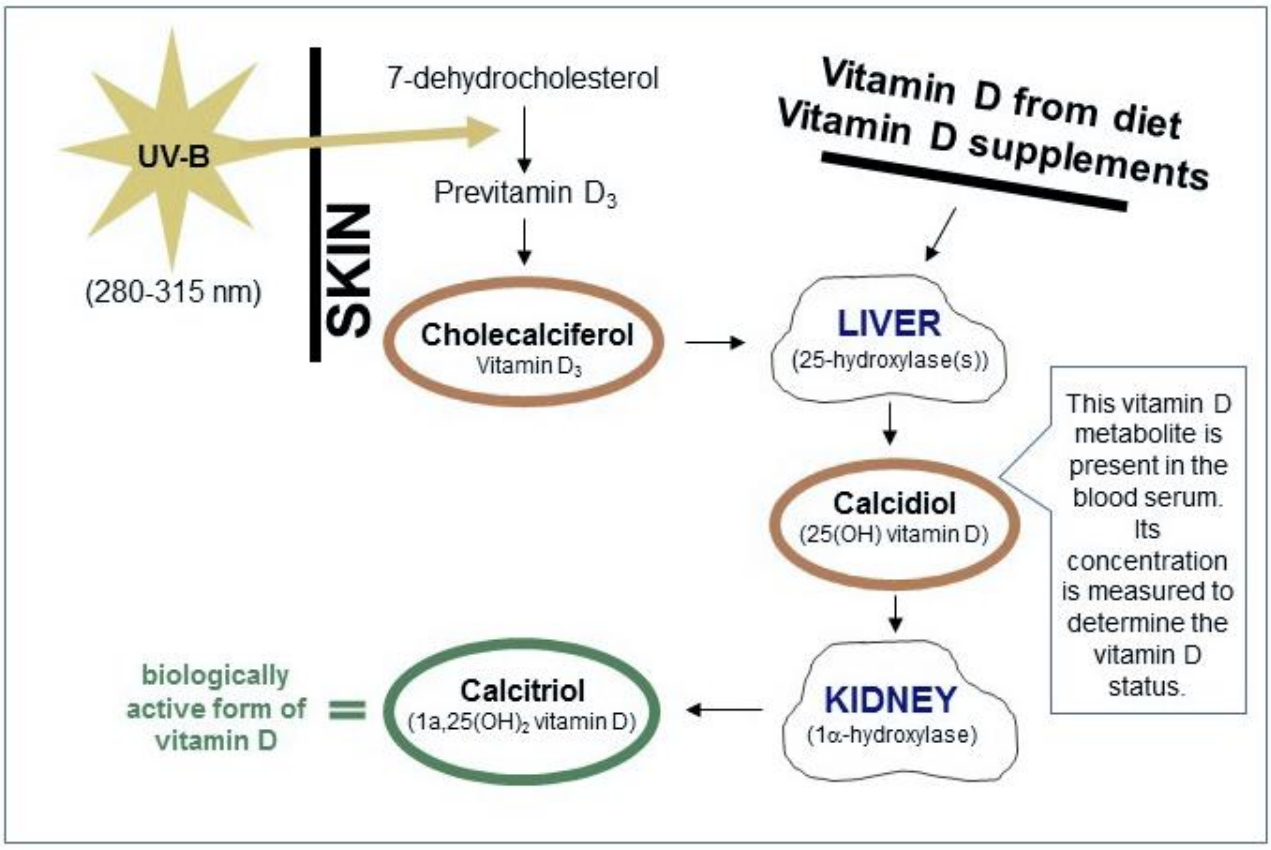

Figure 2: Synthesis of vitamin D

Although vitamin D 2 and D3were considered equally active for many years, current knowledge indicates that the potency of vitamin D2 is less than one-third of that of vitamin D 3 [1-3]. The potential responsible factors are different metabolic pathways and/or different affinity of the active metabolites of vitamins D 2 and D 3 toward vitamin D receptor (VDR). Vitamin D3 is the main form of vitamin D in humans, and indeed, it is estimated that about 80–90% of the vitamin D requirements are covered by the endogenous synthesis in the extent of the skin vitamin D synthesis is dependent on the length of skin sun exposure, the season of the year, and latitude [4]. A 20-min long whole-body exposure to the summer sun is able to produce up to 250 lg of vitamin D 3 [5, 6]. A number of effects are attributed to vitamin D. The most known and studied effect is linked to calcium and phosphate homeostasis, with a crucial impact on bone metabolism. In addition to mineral homeostasis, current research has been investigating a plethora of different activities of vitamin D. VDR, which interacts with the active form of vitamin D, calcitriol or 1,25-dihydroxy-cholecalciferol (1,25(OH) 2 D 3) has been identified in almost all human cells, even in those that do not play a role in calcium metabolism, including the skin, brain, immune cells, prostate cancer cells, and pancreases [7, 8].

Vitamin D and Immunity

While it is well established that vitamin D enhances intestinal calcium absorption, an effect mediated via regulation of calcium transport proteins in the small intestine [9], exhibiting a central role in the its effects on the immune system (Figure 3).

Cells of the immune system harbour the vitamin D activating enzyme 1-α-hydroxylase and express the vitamin D receptor (VDR) [10, 11]. Cells of the immune system which express the VDR and harbour 1-α-ydroxylase are macrophages, T cells, dendritic cells, monocytes, and B cells [12-14] (Figure -4).

Vitamin D is involved both in the regulation of the innate immunity as it enhances the body defense system.

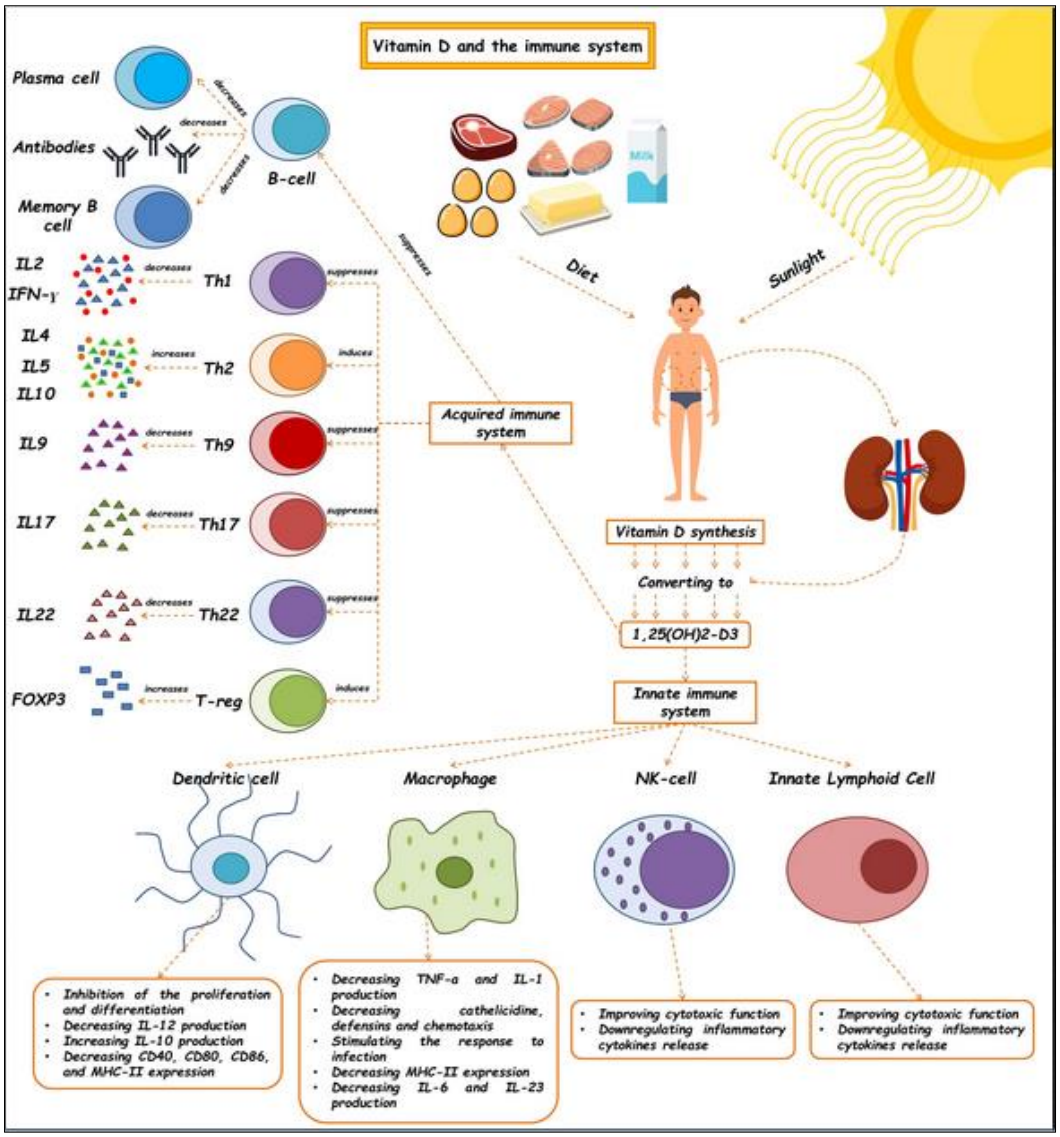

Figure 3: Cells of the immune system which are targets of vitamin D, macrophages, neutrophils, T-lymphocytes, dendritic cells, B lymphocytes

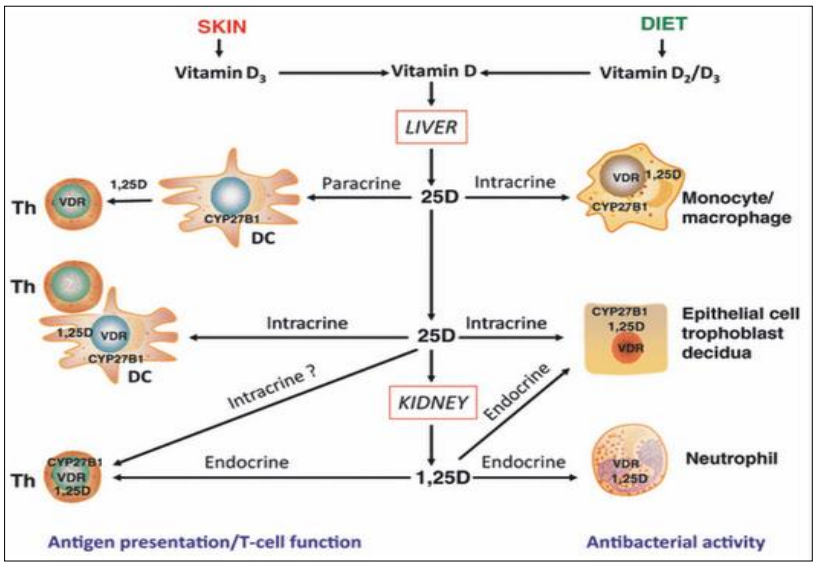

Figure 4: The effects of vitamin D on the immune system

Against microbes and other pathogenic organisms, as well as in the modulation of the adaptive immune system through direct effects on T cell activation and on antigen presenting cells; in particular, dendritic cells.

Vitamin D and the Innate Immune System

Vitamin D regulates the innate immune system [15-17]. The innate immune system - strategy is a first line of defense against infection [18, 19]. Its major functions include recruitment of immune cells, activation of the complement cascade (Figure -5). Identification and removal of foreign substances, activation of the adaptive immune response, and the utilization of physical and chemical barriers against infectious agents [19]. The vitamin D receptor (VDR) is expressed both in the keratinocytes [20, 21], and cells of the innate immune system such as macrophages and monocytes [22-25].

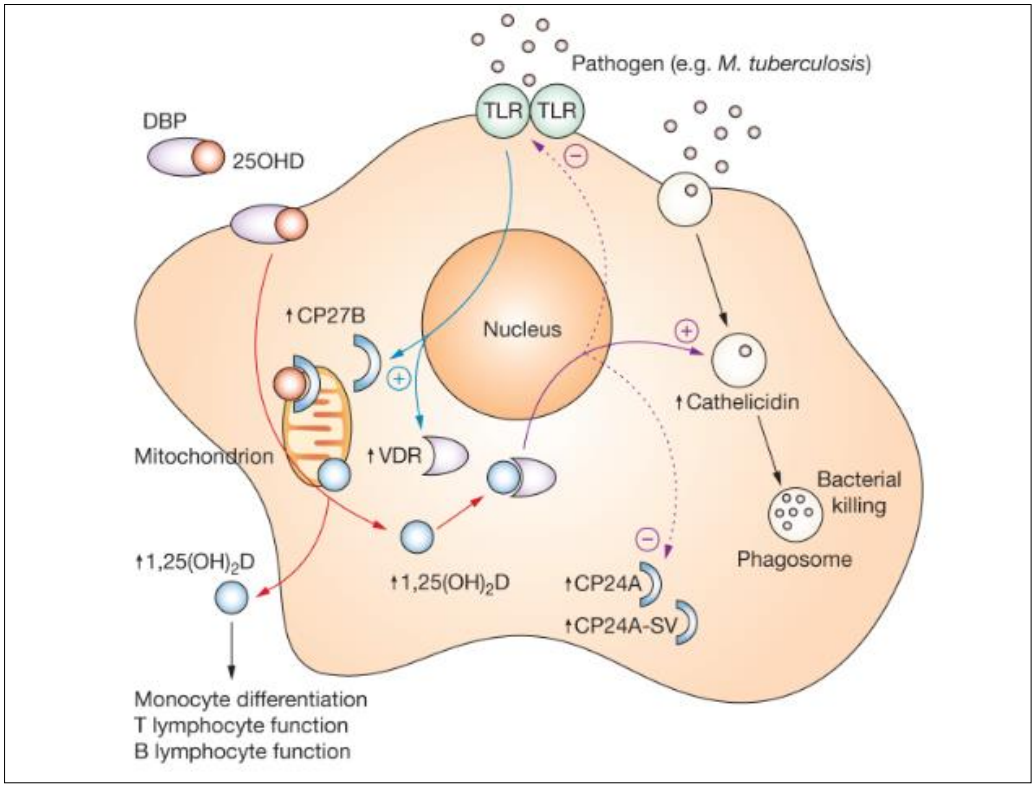

Figure 5: Vitamin D and innate immunity

Vitamin D enhances the production of defensin β2 and cathelicidin in response to infection by macrophages, monocytes, and keratinocytes [26]. Humans have only one cathelicidin [27], which is produced by cells of the immune system, including neutrophils, macrophages, and cells lining epithelial surfaces that are constantly exposed to potential pathogens such as the skin, the respiratory, and the gastrointestinal tract [28-30].

Vitamin D and Adaptive Immunity

Vitamin D acts to regulate the adaptive immune system (Figure-6). The adaptive immune system includes both humeral immunity components and cell mediated immunity components, both directed against invading pathogens. Adaptive immunity leads to immunological memory after an initial response to a specific pathogen, resulting in an enhanced response to future encounters with that pathogen [31]. Vitamin D can promote development and function of Tregs in vitro. Also, effector T cells are directly and indirectly affected leading to a shift in the Th1/Th2 balance towardTh2 and a reduction of the Th17 response [32]. Once T cells are activated, 1,25(OH)2 D3 inhibits IL-2 production [33]. T cells harbour the vitamin D receptor. The behaviour of T cells is modulated by vitamin D indirectly via its effects on dendritic cells. The vitamin D receptor is expressed at low levels in freshly isolated CD8+ and CD4+ T cells [34, 35], vitamin D deficiency results in a reduced capacity to turn off T cells following activation.(36)In a previous study, peripheral blood mononuclear cells which were stimulated with T-cell specific mitogen in the presence of 1,25(OH)2D3 proliferated less and produced less inflammatory cytokines, including interferon-γ [37].

B cells can upregulate the expression of vitamin D receptor and 1a-hydroxylase [38]. 1,25(OH)2 D3 in B cells can induce apoptosis, inhibiting memory B cell formation and preventing differentiation of B cells to immunoglobulin-producing plasma cells [39].

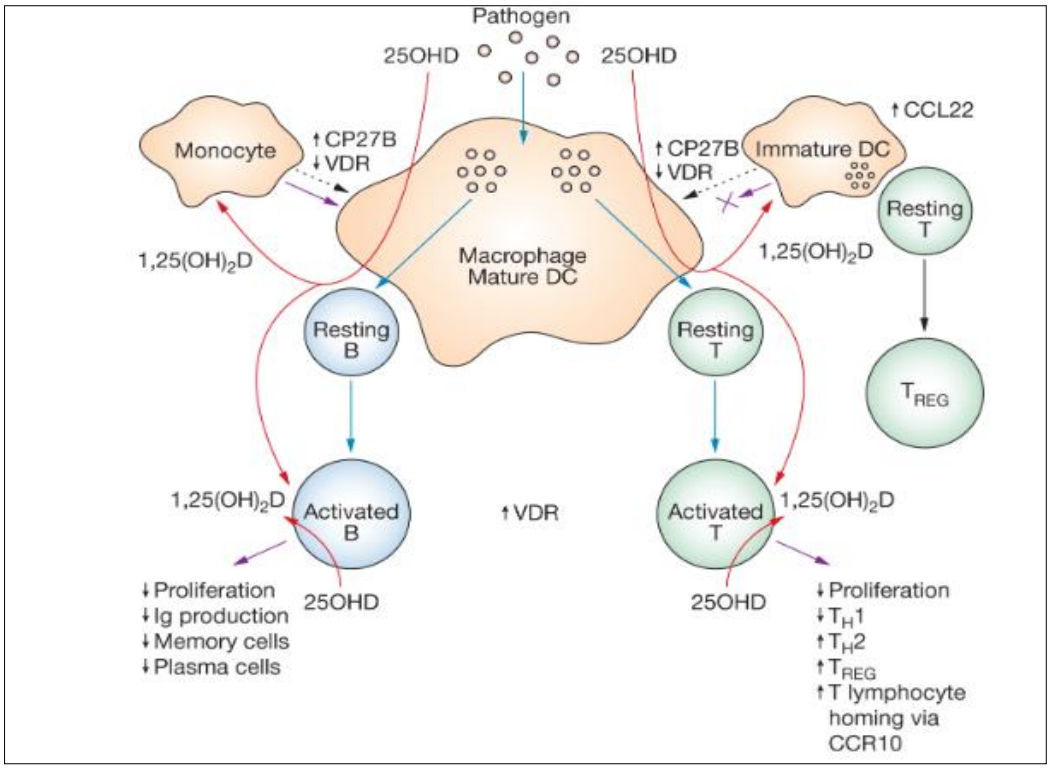

Figure 6: Vitamin D and Adaptive immunity

Vitamin D and Autoimmune Disease

Multiple Sclerosis (MS)

MS is a chronic inflammatory disease characterized by immune-mediated damage of central nervous system [40]. The etiology of MS is not well understood but, like other autoimmune diseases, could be attributed to genetic predisposition and/or environmental factors [41, 42], he prevalence of the disease is lower in equatorial regions and becomes higher with increasing latitudes [43]. This phenomenon could be caused by the lack of sunshine in high-latitude regions that is required for the cutaneous synthesis of vitamin D and suggests that vitamin D insufficiency could be a potential risk factor for MS. Multiple studies also demonstrated that most of the MS patients were deficient in vitamin D [44-46]. In particular, low serum 25 (OH)D levels were associated with high disability and relapse rate in MS patients [44, 45]. However, serum 1,25 (OH)2D, which is the biologically active form of vitamin D, was not directly associated with both disability and relapse rate [45]. Recent studies showed that vitamin D deficiency might increase the risk of MS [47]. As a result, detection of vitamin D deficiency and restoring vitamin D status to adequate levels the clinical trials were unable to provide definitive evidence to support the therapeutic effects of vitamin D intervention, the beneficial effects of oral vitamin D supplementation on MS progression need to be further investigated [48].

Type 1 Diabetes Mellitus (T1DM)

T1DM is an immune-mediated disease that is caused by autoimmune destruction of pancreatic β cells that produce insulin, leading to insulin deficiency [49]. Similar to other autoimmune diseases, environmental factors and/or genetic susceptibility could play roles in the onset and progression of T1DM [50]. The prevalence of vitamin D deficiency/insufficiency was higher in T1DM children compared to controls [51-53]. The strong correlation between vitamin D and T1DM, it has been suggested that vitamin D could prevent the damage, rescue the function of pancreatic β cells, and reduce the incidence of T1DM. Pitocco *et al*., and Li *et al*., both demonstrated that vitamin D had a protective effect on preserving β-cell function [54, 55].

Systemic Lupus Erythematosus (SLE)

SLE is a systemic autoimmune disease that can cause chronic inflammation and damage in multiple tissues and organs [56]. Environmental factors and genetic susceptibility are both responsible for the pathogenesis of SLE [57, 58]. One of such factors is vitamin D deficiency. SLE patients tend to have inadequate vitamin D since most of them are photosensitive to UV radiation and unable to expose themselves to sunlight [59]. The correlation between vitamin D deficiency/insufficiency and SLE has been documented in multiple studies. Some studies suggested that vitamin D concentrations were inversely related to SLE activity [60-62].

Rheumatoid Arthritis

Vitamin D does not play an important role in the pathogenesis of rheumatoid arthritis. This fact was supported by a recent studies, which showed that there are insufficient data to demonstrate the effect of vitamin D on rheumatoid arthritis activity (DAS-28 or pain) or

flares [63]. On the contrary, vitamin D supplementation can be employed to prevent musculoskeletal complications in patients suffering from rheumatoid arthritis with a deficiency of this vitamin.

CONCLUSION

Vitamin D is a likely immunostimulatory or immunomodulatory agent. It has immune stimulating properties, as it enhances the function of the innate and Adaptive immune system. Vitamin D deficiency or insufficiency is associated with compromised immunity, leading to increased infectious diseases such as tuberculosis, and increased susceptibility to autoimmune diseases such as type 1 diabetes, Rheumatoid arthritis, systemic Lupus Erythematosus and others.

Conflicts of Interest: The authors declare no conflicts of interest.

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