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Commentary

Is there any evidence in support of the protective role of vitamin D and omega 3 fatty acids on the advance of autoimmune disease?

Running title: Vitamin D confers protection from autoimmunity

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Abstract
Vitamin D has long been regarded as an immunomodulator with the potential to suppress autoreactive immune responses. Its role as a possible protective factor for the future development of overt autoimmune disease remains a matter of ongoing debate. In the clinical setting, it is very difficult to dissect the exact role, if any, of vitamin D, either in the induction or in the progression of autoimmune disorders. However, recent evidence has raised great expectations. The VITAL study recruited more than 25,000 older adults in the USA and provided data suggesting that daily supplementation with 2,000 IU/day of vitamin D, or its combination with omega 3 fatty acids for a total of five years induced a significant reduction in the incidence of specific autoimmune diseases. Herein, we further discuss the noteworthy findings of this study and its wider implications for the management of patients at risk of developing autoimmune disorders.

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I. INTRODUCTION

Vitamin D is long regarded as a potent immunoregulator, able to interact with pro-inflammatory and anti-inflammatory cell subsets and mediators (1). Vitaming D and its metabolites are largely derived from the exposure to ultraviolet light on the skin, which converts the prodromal vitamin D to vitamin D_3. In the liver, vitamin D-25 hydroxylase generates the 25-hydroxyvitamin D (25D), which is metabolised to the active form of 1.25-dihydroxyvitamin D (1.25D) which in turn, binds with the vitamin D Receptor (VDR). The fact that T cells, dendritic cells, macrophages and even B cells express VDR has led several investigators to consider 1.25D as an essential factor for the regulation of the immune system (1, 2). Recent evidence suggests that the general population, including patients with autoimmune diseases, either organ-specific or non- specific, experience a significant deficiency of vitamin D, and that the circulating levels of 1.25D may inversely correlate with disease activity (3-6). On the other hand, this deficiency is not always the prerequisite for the development of an autoimmune disease, but can serve as a marker of an autoimmunity-induced consequence or disease progression (6-12). Although debates are still apparent on whether vitamin D deficiency is an epiphenomenon or participates in complex immunological phenomena leading to the induction of autoimmunity, a consensus has been reached regarding the status of most affected patients at the time of diagnosis, the great majority of whom demonstrate low vitamin D levels (6). Unarguably, this has led to the extreme end, an overconsumption of vitamin D supplements irrespectively of whether the affected individual has normal or abnormal vitamin D concantrations (13). In fact, over-the-counter supplements of vitamin D have become so popular, that it has become highly likely for older adults to report consuming vitamin D oral nutrient supplements (ONS) on a

daily basis and for a significant period of time, even in absence of osteopenia or osteoporosis (13).

Since the deficiency of vitamin D_3 is a characteristic feature of patients with autoimmune diseases, the question arises on whether these patients would be protected from the disease, if vitamin D_3 concentrations were normal or elevated (1, 6). Is vitamin D_3 defficiency *per se* adequate for the primary prevention against autoimmune diseases? At what levels would this protection be tenable? These questions have been addressed in various animal models of autoimmune diseases, including autoimmune encephalomyelitis, multiple sclerosis (1), inflammatory bowel diseases, rheumatoid arthritis and type 1 diabetes mellitus (1, 6).

A large primary prevention trial (VITAL), conducted in older Americans was designed to answer these questions (14, 15). VITAL was a randomized, double-blind, placebo-controlled trial of 25,871 men and women across the USA. The study explored whether the daily intake of ONS of vitamin D_3 (2,000 IU) or omega-3 fatty acids could decrease the risk for developing chronic diseases such as cancer, heart disease and stroke in people who do not have a prior history of such diseases (15). The participats were randomized into four arms, with participants receiving a) vitamin D and omega-3 fatty acid ONS, b) vitamin D ONS and a placebo, c) omega-3 fatty acid ONS and a placebo, d) or placebo only. According to the authors "*supplementation with vitamin D at the dose of 2,000 IU/day for approximately five years, alone or in combination with 1 g/day of omega 3 fatty acids (460 mg eicosapentaenoic acid and 380 mg docosahexaenoic acid) led to a lower incidence of confirmed autoimmune disease than placebo*"(14). However, supplementation with omega-3 fatty acids alone failed to lower the incidence of autoimmune diseases, suggesting that it was, in fact, vitamin D ONS rather than omega-3 fatty acids, which accounted for the observed decrease in the the incidence (14).

A sub-analysis of the data provided further clues regarding the relevance of omega-3 fatty acids ONS to autoimmunity prevention. The analysis that included participants with probable autoimmune disease revealed that omega-3 fatty acid ONS reduced the rate of autoimmune diseases by 18% compared to placebo (14). Another interesting point was that when only the last three years of the intervention were accounted for, the group supplemented with vitamin D had 39% fewer cases with a confirmed diagnosis of an autoimmune disease than the placebo group (14). Finally, supplementation with both vitamin D and omega-3 fatty acids decreased the incidence of autoimmune disease by about 30% versus placebo alone. Among the various autoimmune diseases, the incidence of rheumatoid arthritis was approximately 40% lower in the supplementation arms than in the placebo groups. These results must be treated with caution, as less than 40 participants had a definite diagnosis (14).

Furthermore, these findings need external validation. As the trial tested only one dose and formulation of each supplement, it is not clear whether there is a dose-dependent effect, or if the decrease could be noted irrespectively of the dosage of the tested supplements. Moreover, the issue is further perplexed by both the low sample size of patients diagnosed with autoimmune diseases and the uncertainty in the diagnosis of some cases (14). In addition, the duration of the trial may also raise more issues; five years may not be an adequate period, as the preclinical phase of several autoimmune diseases can last for several years, or even decades.

Nevertheless, the findings of this study are of importance for the management of individuals who are at high risk for the development of autoimmune disease, such as family members of patients with autoimmune diseases, or individuals with a genetic background who are prone to develop autoimmune diseases (9). Can we recommend supplementation with vitamin D and omega 3 fatty acids as early as possible and long before the signs of autoimmunity are apparent? Can we recommend in high-risk individuals the regular assay of vitamin D concentrations? Do we need to issue recommendations or guidelines regarding protective measures which could include supplementation with vitamin D and omega 3 fatty acids (9)?

II. CONCLUSIONS

Several areas for improvement are apparent regarding the design and execution of nutrition supplementation trials for the prevention of autoimmune disorders. An adequate sample size and robust diagnostic procedures are needed for future research. Special populations, such as the young and individuals at high risk for developing autoimmunity could also be included in future studies.

AUTHORS CONTRIBUTIONS

DPB and MGM had the original idea and scripted the original draft and subsequent drafts; DA and KG scripted parts of the manuscript and reviewed the literature. All authors approved the final version

of the manuscript.

CONFLICT OF INTEREST

All Authors declare no conflict of interest.

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