European Review for Medical and Pharmacological Sciences 2022; 26: 6787-6795

The importance of vitamin D and omega-3 PUFA supplementation: a nonpharmacologic immunomodulation strategy to halt autoimmunity

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Abstract. – The large, randomized, double-blind, placebo-controlled trial VITAL (Vitamin D and omega 3 trial) recently confirmed that vitamin D and omega-3 polyunsaturated fatty acid (PUFA) co-supplementation (VIDOM) can reduce the incidence of autoimmune diseases. Based on these relevant results, this commentary summarizes the molecular mechanisms behind the anti-inflammatory and immunomodulatory properties of vitamin D and omega-3 PUFAs. We also describe the potential bidirectional interplay between vitamin D metabolism and omega-3 PUFA metabolism that underlies the rationale for VIDOM co-supplementation and that may contribute to enhance the anti-inflammatory and immunomodulatory actions of vitamin D and omega-3 PUFAs when these compounds are administered in combination.

Key Words:
Autoimmune diseases, Autoimmunity, Immunomodulatory nutrition, Nutritional immunology, Omega-3 PUFAs, Prevention, Treatment, Vitamin D.

Introduction

We are writing the present commentary in light of the recent relevant results of the large, randomized, double-blind, placebo-controlled trial VITAL (Vitamin D and omega 3 trial) that was conducted in the United States and investigated whether vitamin D and omega-3 polyunsaturated fatty acids (PUFAs) reduce autoimmune disease risk[1]. In this study, vitamin D was administered as cholecalciferol (vitamin D3) at a dose of 2000 IU/day, whereas marine omega 3 PUFAs were administered at a dose of 1 g/day (as a fish oil capsule containing 460 mg of eicosapentaenoic acid and 380 mg of docosahexaenoic acid). The trial included 25,871 participants, consisting of 12,786 men ≥50 years and 13,085 women ≥55 years at enrollment. Participants were followed for a median period of 5.3 years. During this follow-up period, participants self-reported all incident autoimmune diseases from baseline, and these diseases were confirmed by extensive medical record review. For the vitamin D arm, 123 participants in the treatment group and 155 participants in the placebo group had confirmed autoimmune disease (adjusted hazard ratio 0.78, 95% confidence interval 0.61 to 0.99, p-value=0.05). For the omega-3 PUFA group, confirmed autoimmune disease occurred in 130 participants in the treatment group and in 148 participants in the placebo group (adjusted hazard ratio 0.85, 95% confidence interval 0.67 to 1.08, p-value=0.19). Thus, 5-year vitamin D supplementation, with or without omega-3 PUFAs, reduced autoimmune disease by 22%, whereas omega-3 PUFA supplementation, with or without

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vitamin D, reduced the autoimmune disease rate by 15% (although this reduction was not statistically significant). Nevertheless, both treatment arms showed larger effects than the reference arm (consisting of vitamin D placebo and omega-3 PUFA placebo)[1]. These results confirmed our previous hypothesis and preliminary findings of beneficial effects of vitamin D and omega-3 PUFA co-supplementation (VIDOM) in the context of autoimmune diseases[2-5].

The Autoimmune Pandemic

Autoimmune diseases represent a family of at least 80 different conditions resulting from an abnormal response of the immune system that ultimately leads to the destruction of specific body's own tissues and organs[6]. Epidemiologic data provide evidence of a steady rise in the incidence and prevalence of autoimmune diseases over the last three decades[7]. Importantly, autoimmune conditions are associated with a significant disease burden due to their chronic nature and the frequent need for lifelong use of disease-modifying therapies such as immunomodulatory and/or immunosuppressive drugs that are not devoid of potential short-term and long-term side effects. Although the etiology and pathophysiology of autoimmune diseases is not fully understood, the development of such conditions typically requires the concomitant presence of genetic predisposition and environmental factors (e.g. dietary factors, infections, medications, among others) that trigger immune pathways leading to tissue destruction[8]. At the present time, there are no known effective therapies able to recude the incidence and to prevent the development of autoimmune diseases. Hence, there is a great parallel need for nonpharmacologic and nutrition strategies able to halt this dangerous trend. In this regard, the recent results of the VITAL study[1] are of high clinical significance, since both vitamin D and omega-3 PUFAs are safe, well-tolerated, nontoxic and inexpensive nutritional supplements that may be particularly beneficial in high-risk individuals carrying one or more risk factors for development of autoimmune diseases (e.g. female sex or known family history of autoimmune diseases).

The global incidence of autoimmune diseases is approximately 3-5% and is increasing particularly in Westernized countries due to to the shift from traditional dietary patterns towards Westernized patterns ("nutrition transition")[9,10]. This prompted the scientific community to investigate possible nutritional interventions aimed to reduce the risk of autoimmune diseases[10]. It has been postulated that the rapid increase in the incidence of autoimmune diseases in developed countries and in migrant populations may be the consequence of environmental factors rather than genetic factors[10]. A pathophysiological hypothesis explaining this trend in Westernized countries is the so-called "*leaky gut syndrome*", a condition characterized by increased gut permeability, altered integrity of human intestinal epithelial barrier, tight junction dysfunction, and alteration in gut microbiota composition. Leaky gut syndrome favours local and systemic inflammation. The resulting malabsorption increases the risk for deficiency of different macronutrients and micronutrients such as vitamin D deficiency, which has been associated with an increased risk of autoimmune diseases[10-14]. It is also worth reminding that the intestinal epithelial barrier controls the equilibrium between tolerance and immunity to nonself-antigens through its intercellular tight junctions[15]. Dysregulation of the finely tuned trafficking of macromolecules in genetically susceptible individuals can lead to both intestinal and extraintestinal autoimmune disorders[15]. Leaky gut syndrome is probably caused by industrial food additives commonly used in the current Westernized diets and processed foods[10,16,17]. Moreover, a Westernized food regime is rich in saturated fats and omega-6 PUFAs, wich exert pro-inflammatory properties and may increase the risk of developing autoimmune diseases[10,18,19]. On the other hand, anti-inflammatory diets, that are rich in fibers and omega-3 PUFAs (like the Mediterranean diet), might prevent the leaky gut syndrome and preserve the integrity of intestinal epithelial barrier as well as the gut microbiota composition, which may result in the prevention of autoimmune diseases and other chronic noncommunicable diseases[10,18,20].

Vitamin D and Autoimmune Diseases

Over the last three decades, it has become clear that the role of vitamin D goes beyond the regulation of bone and calcium homeostasis[12,21]. Indeed, vitamin D exerts a series of anti-infective, anti-inflammatory and immunomodulatory properties by acting on the vitamin D receptor (VDR), which has been identified in almost all immune cells[22-24]. These properties involve: i) the inhibition of production of pro-inflammatory cytokines[25]; ii) the reduction of the antigen-presenting capacity and T-cell stimulatory ability by antigen presenting

cells[26-32]; iii) the upregulation of regulatory T cells (Tregs)[33]; iv) the promotion of the shift of T-cell effector phenotype (Th1 and Th17 cells) towards a regulatory anti-inflammatory phenotype (Th2)[34-36]; v) the promotion of the transition from pro-inflammatory interferon-gamma (IFN-γ)-secreting Th1 cells to suppressive interleukin-10-producing cells[37]; and vi) the promotion of the shift of macrophage polarization from the pro-inflammatory M1 phenotype towards the M2 anti-inflammatory phenotype[38]. Besides being vitamin D targets, immune cells (macrophages, dendritic cells, T- and B-lymphocytes) represent also local producers of vitamin D, as they express the key vitamin D-activating enzymes 25-hydroxylase and 1α-hydroxylase that catalyze the local conversion of inactive vitamin D precursors into the biologically active form calcitriol[39].

Vitamin D deficiency currently represents a global pandemic afflicting more than one billion individuals across all age groups[40]. A growing body of evidence suggests that vitamin D deficiency may play a role in the pathophysiology of different autoimmune and inflammatory diseases such as type 1 diabetes, multiple sclerosis, systemic lupus erythematosus and rheumatoid arthritis, among others[11-13]. Therefore, vitamin D supplementation has been proposed and investigated as a potential valid adjuvant immunomodulatory treament for the aforementioned conditions[11]. An important aspect to be considered is the optimal circulating vitamin D concentration aimed at achieving the anti-inflammatory and immunomodulatory actions exerted by calcitriol. Emerging evidence suggests that serum 25-hydroxyvitamin D [25(OH)D] levels ≥40 ng/mL (slightly above those deemed as sufficient for bone health) are optimal to achieve the anti-infective, anti-inflammatory and immunomodulatory properties of vitamin D in vivo[12,24,41,42]. In this regard, a dietary and/or supplemental intake of vitamin D3 of 4000-6000 IU/day is generally safe and effective in reaching and maintaining such circulating 25(OH)D concentrations in adults[42].

Omega-3 PUFAs, Omega-6 PUFAs and Autoimmune Diseases

Over the last decades, Western diets have progressively evolved towards an increased amount of omega-6 PUFAs compared to omega-3 PUFAs. Omega-3 and omega-6 PUFAs are known to exert anti-inflammatory and pro-inflammatory properties, respectively[18,43]. The omega-6 PUFA arachidonic acid (AA) is the precursor of the pro-inflammatory eicosanoids (prostaglandins, thromboxanes and leukotrienes), which mediate the initiation of acute inflammation and play an important role in the modulation of endothelial permeability, neutrophil chemotaxis and platelet aggregation[43-45]. Conversely, omega-3 PUFAs play an anti-inflammatory role by displacing AA in membrane phospholipids, reducing the synthesis of pro-inflammatory eicosanoids, and favouring the resolution of inflammation, as they represent the precursors of a group of lipid mediators which are collectively termed "specialized pro-resolving mediators" (SPMs). SPMs include resolvins, protectins and maresins[46]. SPMs are produced by polymorphonuclear neutrophils (PMN) and macrophages during the resolution of inflammation, promoting key cellular events such as macrophage switching to anti-inflammatory phenotype M2, cessation of PMN infiltration and apoptotic cell clearance[46,47]. SPMs have also emerged as endogenous modulators of oxidative stress[48]. The omega-3 long-chain PUFA eicosapentaenoic acid [EPA, 20:5 (n-3)] is the precursor of the E-series resolvins (RvE1, RvE2, and RvE3), while the omega-3 long-chain PUFA docosahexaenoic acid [DHA, 22:6 (n-3)] leads to the generation of three distinct families of SPMs, namely D-series resolvins (RvD1, RvD2, RvD3, RvD4), protectins (protectin D1, a.k.a. neuroprotectin D1 when formed in the nervous system), and maresins[46,49].

Increased circulating values of omega-6/omega-3 ratio and AA/EPA ratio have been proposed as biomarkers of systemic inflammation[50-53]. The optimal AA/EPA ratio value to reduce cellular and systemic inflammation should be between 1.5 and 3, although it is typically higher in industrialized countries (e.g., it is 18 in the average American population) due to the high consumption of Westernized diets[18].

Mounting evidence obtained from genetic mouse models and clinical studies has shed light on the functions and the mechanisms of omega-3 PUFAs and their metabolites in the prevention and treatment of different autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and type 1 diabetes[54]. In this regard, Löfvenborg et al[55] recently showed that individuals with high levels (≥167.5 units/mL) of the islet autoantibody glutamic acid decarboxylase (65-kDa isoform, GAD65) and low total plasma phospholipid n-3 PUFAs had a more than fourfold higher hazard of diabetes compared with antibody-negative subjects with high n-3

PUFA concentrations, suggesting that high fish intake or relative plasma phospholipid n-3 PUFA concentrations may partly reduce the increased diabetes risk conferred by GAD65 antibody positivity.

Many of the beneficial effects of omega-3 PUFAs have been traced back to their anti-inflammation actions, even through the regulation of mTOR (mammalian target of rapamycin) activity[54]. Rapamycin (the inhibitor of mTOR) has been shown to inhibit the proliferation of T cells as well as the differentiation to Th1 cells[56], and to promote the differantiation of naive CD4+ T cells into Tregs[57]. It has been shown that omega-3 and omega-6 PUFAs have an opposite impact on the regulation of mTOR complexes, thereby dictating the differentiation fate of CD4+ T cells following PUFA treatment. EPA and DHA decreased the phosphorylation of ribosomal protein S6 (indicative of inhibition of mTORC1 activity), whereas the omega-6 AA increased S6 protein phosphorylation levels by activating mTORC1 (mammalian target of rapamycin complex 1)[19,54,58]. Moreover, D-series resolvins (RvD1 and RvD2) and maresin 1 (MaR1) have been shown to modulate adaptive immune responses in human peripheral blood lymphocytes, reducing cytokine production by activated CD8+ T cells and Th1 and Th17 cells and preventing naïve CD4+ T-cell differentiation into Th1 and Th17, without modulating T-cell inhibitory receptors or abrogating their capacity to proliferate[59]. These mechanisms have important implications for autoimmune diseases. For instance, it has been shown that SPMs are differentially altered in peripheral blood of patients with multiple sclerosis, with the majority of these mediators being significantly reduced and correlating with disease progression[60]. These findings suggest SPMs as novel diagnostic biomarkers and potentially safe therapeutic agents for autoimmune disorders.

The Rationale for VIDOM Co-Supplementation is Based on Potential Bilateral Interplay Between Vitamin D and Omega-3/Omega-6 PUFA Metabolism

In light of the above, hypovitaminosis D and omega-3 PUFA deficiencies may represent key environmental risk factors for development of autoimmune diseases. Indeed, vitamin D and omega-3 PUFA deficiencies can be associated with an increase in systemic inflammation[12,22,61]. Vitamin D and omega-3 PUFAs, when administered in combination (as VIDOM co-supplementation), may exert synergistic anti-inflammatory and imunomodulatory actions to a greater extent than when they are administered alone. In fact, adequate circulating vitamin D and omega-3 PUFA concentrations may contribute to reduce systemic inflammation by enhancing a systemic anti-inflammatory state. Accordingly, preliminary intervention studies and clinical trials demonstrated that VIDOM co-supplementation leads to significant benefits in different clinical settings, including insulin resistance and non-alcoholic fatty liver disease[62], prediabetes[63], type 2 diabetes mellitus associated with coronary heart disease[64], gestational diabetes mellitus[65,66], polycystic ovary syndrome[67], type 1 diabetes mellitus[2,3,5,13,68], inflammatory bowel disease[69], and autism spectrum disorder[70]. Such beneficial effects likely arise from the synergistic anti-inflammatory, antioxidant and immunomodulatory properties exerted by vitamin D and omega-3 PUFAs. With this regard, it is plausible that interactions between vitamin D metabolism and omega-3/omega-6 PUFA metabolism exist. Interestingly, a study conducted by Nandi and colleagues[71] on pregnant female rats demonstrated that animals with vitamin D deficiency exhibited higher blood and liver AA levels compared to control animals with normal dietary levels of vitamin D. This was accompanied by a higher plasma Δ5-desaturase activity index[71]. Δ5-desaturase is a rate-limiting enzyme in PUFA synthesis, it is expressed primarily in the liver and catalyzes the synthesis of the pro-inflammatory omega-6 PUFA AA and of the omega-3 PUFA EPA by introducing double-bonds to the delta-5 position in the fatty acid chain[72]. These findings suggest that maternal vitamin D deficiency influences fatty acid desaturase activity and expression, thereby altering maternal fatty acid metabolism. In addition, a study conducted in 5/6 nephrectomy rats showed that omega-3 PUFAs and vitamin D3 (cholecalciferol) may synergistically increase 1,25-dihydroxyvitamin D [1,25(OH)2D] levels by inhibiting the expression of the vitamin D-catabolizing enzyme 24-hydroxylase in the kidney and in the liver, and by upregulating the expression of the vitamin D-activating enzyme 1α-hydroxylase in the liver[73]. These findings suggest that omega-3 PUFAs can modulate vitamin D metabolism and activation. Moreover, these findings may also explain the results from a previous study that reported a significant increase in circulating 1,25(OH)2D levels after 6-month omega-3 PUFA supplementation in dialysis patients[74].

Another pilot study conducted in hemodialysis patients with hypovitaminosis D showed that 12-week administration of cholecalciferol plus omega-3 PUFAs led to a higher ratio of 1,25(OH)2D to 25(OH)D (which reflects the activation of the enzyme 1α-hydroxylase), as compared to the group receiving cholecalciferol plus olive oil, although this change was not significant[75]. This may suggest that supplementation with omega-3 PUFAs, including DHA, may be better than the control treatment in terms of regulating 1,25(OH)2D levels[75]. A recent systematic review and dose-response meta-analysis of ten randomized controlled trials evaluating the influence of omega-3 PUFA supplementation on 25(OH)D levels showed an overall significant increase in 25(OH)D levels following omega-3 PUFA intake[76]. Authors also found that 25(OH)D levels were significantly increased when the intervention duration lasted >8 weeks and when the baseline serum 25(OH)D concentration was <20 ng/mL[76].

Figure 1 shows the potential bidirectional interplay between vitamin D metabolism and omega-3/omega-6 PUFA metabolism (inferred from animal and clinical studies) that may contribute to enhance the anti-inflammatory and immunomodulatory actions of vitamin D and omega-3 PUFAs upon VIDOM co-supplementation.

Conclusions

VIDOM co-supplementation holds great promise as a potential, safe, inexpensive and effective approach for prevention and treatment of autoimmune disorders and immune-mediated conditions, that currently pose a significant economic and health burden worldwide. This hypothesis has recently been confirmed by the large, randomized-controlled trial VITAL, that investigated the effectiveness of vitamin D3 (at a dose of 2000 IU/day) plus omega-3 PUFAs (at a dose of 1 g/day) in preventing autoimmune diseases[1]. With regard to the VITAL study, it is also plausible that higher vitamin D and omega-3 PUFA doses (aimed to achieve optimal circulating 25-hydroxyvitamin D and AA/EPA ratio values) may have led to even better results. The beneficial effects of vitamin D and omega-3 PUFAs on autoimmunity may be mediated by their synergistic anti-inflammatory and immunomodulatory properties. Indeed, these

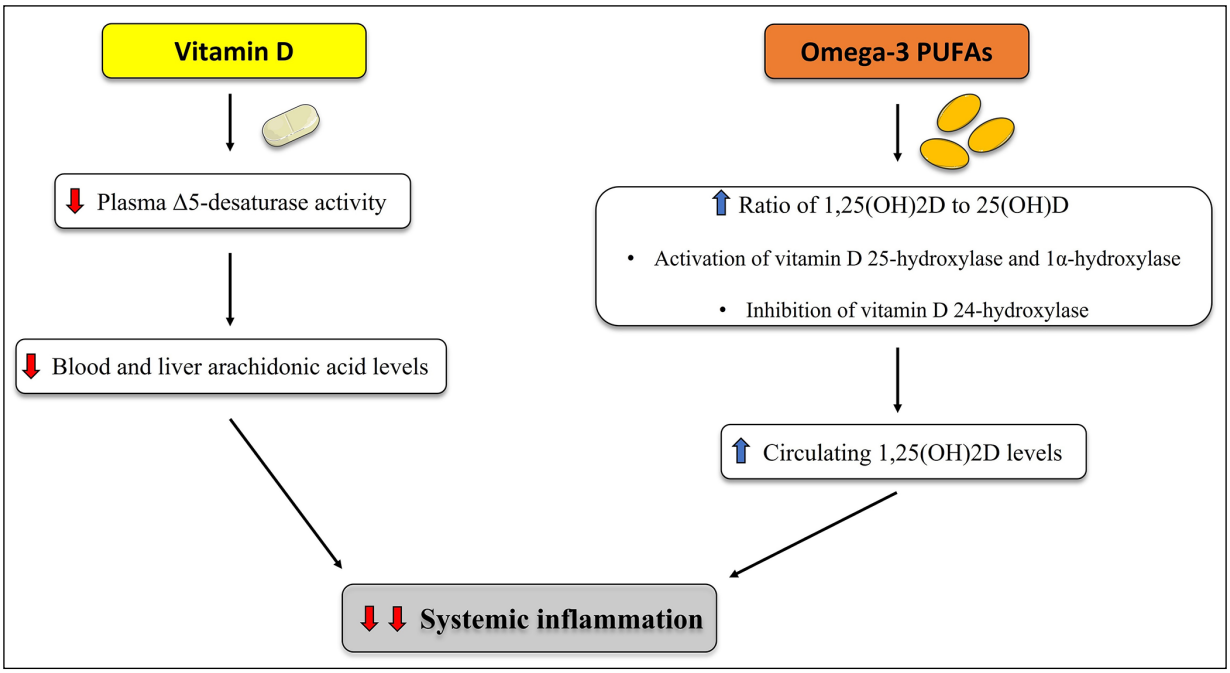

Figure 1. Potential bidirectional interplay between vitamin D metabolism and omega-3/omega-6 PUFA metabolism (inferred from animal and clinical studies) that may contribute to enhance the anti-inflammatory and immunomodulatory actions of vitamin D and omega-3 PUFAs upon VIDOM co-supplementation. Abbreviations: 1,25(OH)D2, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; PUFAs, polyunsaturated fatty acids; VIDOM, vitamin D and omega-3 PUFA co-supplementation. The figure was partly created with images adapted from Servier Medical Art licensed under a Creative Commons Attribution 3.0 Unported License (https://smart.servier.com/).

properties are likely to be enhanced when these compounds are administered together, given the bidirectional interplay existing between vitamin D metabolism and omega-3/omega-6 PUFA metabolism. Therefore, a better mechanistic understanding of vitamin D and omega-3 PUFA interactions and actions will certainly pave the way for a new therapeutic area in the field of immunomodulatory nutrition.

Conflict of Interest

The Authors declare that they have no conflict of interest.

Funding

The authors received no honorarium, grant or financial support for the research, authorship, and/or publication of this article.

Authors' Contribution

Marco Infante wrote the manuscript. Andrea Fabbri, David Della-Morte and Camillo Ricordi revised and edited the manuscript. All authors read, edited and approved the final version of the manuscript.

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