Could combating vitamin D deficiency reduce the incidence of autoimmune disease?


Vitamin D is a steroid hormone with pleiotropic effects. In addition to its essential role in calcium homeostasis, vitamin D has many nonskeletal effects that are important in health and disease [1]. Although some foods are fortified with vitamin D, the primary source for humans is exposure of skin to ultraviolet B radiation in sunlight. There is increasing evidence that vitamin D may have a role in immunoregulation. 1,25-(OH)$_2$D is the biologically active form of vitamin D. Cells of the adaptive immune system express vitamin D receptors and are sensitive to the action of 1,25-(OH)$_2$D. High levels of 1,25-(OH)$_2$D inhibit dendritic cell maturation with lower expression of MHC class II molecules, downregulation of costimulatory molecules and lower production of proinflammatory cytokines [2,3]. In mouse models, 1,25-(OH)$_2$D drives the adaptive immune system from a Th1/Th17 response toward a Th2 and regulatory T-cell response, suggesting potential beneficial effects of supplementary dietary vitamin D on the occurrence and progression of Th1-mediated autoimmune diseases in humans [4]. The immune system of vitamin D receptor-deficient mice is grossly normal but shows increased susceptibility to autoimmune diseases such as inflammatory bowel disease or Type 1 diabetes [5]. In addition, there is some evidence that vitamin D might play a regulatory role in autoantibody production by B cells, inhibiting the ongoing proliferation of activated B cells and inducing their apoptosis [6]. A common theme in the proposed immunomodulatory functions of vitamin D is that higher levels are immunosuppressive, consistent with a role for vitamin D insufficiency in the pathogenesis of autoimmune disorders.

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Vitamin D has been studied as a modifiable environmental factor in autoimmune diseases, including connective tissue diseases (CTDs) [7–10]. Vitamin D appears to be important for autoimmune disease susceptibility and severity [11–13]. Recently, the epidemiological evidence of an increased multiple sclerosis (MS) risk among individuals with low vitamin D concentrations has achieved substantial strength [14]. In systemic lupus erythematosus (SLE), approximately two-thirds of patients are vitamin D deficient, and 20% have critically low levels of 25-(OH)D$_3$, the form of vitamin D commonly measured in the serum [15,16]. Disease activity in SLE has been associated with vitamin D levels, and vitamin D supplementation has led to attenuation of disease manifestations in experimental models [7]. Patients with undifferentiated CTD [16] and rheumatoid arthritis [17] have been shown to have lower serum 25-(OH)D$_3$ compared with healthy controls, even after controlling for activity level and dietary intake. In rheumatoid arthritis, activity level and
joint pain have been associated with vitamin D levels [18]. In patients with undifferentiated CTD, Zold et al. found that those with lower levels evolved to a more differentiated clinical phenotype [16]. These observations suggest that vitamin D deficiency could be involved in the pathogenesis and end-organ dysfunction of these autoimmune disorders.

Although the association of hypovitaminosis D with CTD appears to be consistent, it is unclear whether vitamin D is an etiologic factor or a marker of disease severity. Disability-related inactivity and reduced sunlight exposure are possible explanations for low 25-(OH)D₃ levels. In addition, medications used to treat CTD, such as corticosteroids, have been shown to increase the consumption of vitamin D, thereby lowering serum levels [19]. In addition to possible confounding factors, many of the available observational studies linking vitamin D deficiency and autoimmune disease are prone to several sources of bias, including selection bias (i.e., bias resulting from selection of a control group with a distribution of exposure that differs from that of the population that generated the cases), reverse causation, and recall bias [14]. We compared vitamin D levels in patients with CTD-related interstitial lung disease (CTD-ILD) with patients with idiopathic forms of ILD. Levels of 25-(OH)D₃ were lower in those with CTD-ILD than in those with idiopathic ILD, even after adjustment for confounding factors [20]. By using a control population with a similar disease state, our findings imply that vitamin D deficiency may be specifically related to the underlying autoimmune disorder.

“There are a number of unresolved clinical questions related to vitamin D and autoimmune disorders. Does aggressive vitamin D supplementation in patients with CTD change the disease outcome? In animal models of SLE, vitamin D administration has been shown to attenuate some disease manifestations [7], however, these findings have not yet been replicated in humans. The target therapeutic levels of vitamin D with supplementation remain undefined. Although it is generally accepted that 25-(OH)D₃ levels below 20 ng/ml represent deficiency, a precise goal for serum level and whether to treat those with vitamin D insufficiency (<30 ng/ml) has not been established. As the risk of vitamin D toxicity is likely to be low with conventional supplementation dosing, many providers target higher levels (>40 ng/ml), but there is no direct evidence to definitively support such an approach.

Practice recommendations
In the absence of clinical trial data, we have adopted the following practice in our approach to patients with CTD-ILD at our ILD center. Patients are routinely screened with serum 25-(OH)D₃ levels. After a discussion of the potential risks and benefits, those patients with serum 25-(OH)D₃ levels of less than 30 ng/ml are offered replacement, particularly if they have been treated with corticosteroids or have risk factors for osteoporosis. Our therapeutic regimen consists of ergocalciferol (vitamin D₃) 50,000 IU once weekly for 8 weeks. Serum 25-(OH)D₃ levels are then rechecked at 8 weeks, with a target of 40 ng/ml. Once the targeted serum 25-(OH)D₃ levels are achieved, cholecalciferol (vitamin D₃) is continued at 2000 IU per day. It is our experience that maintenance of normal 25-(OH)D₃ levels after the initial replacement can be challenging, so levels are frequently rechecked once the maintenance regimen is initiated.

Conclusion
Vitamin D has sparked considerable interest as a modifiable environmental factor in autoimmune diseases. There is preliminary evidence that vitamin D deficiency could be causally related to a variety of autoimmune diseases. Future studies should evaluate whether supplemental vitamin D administration prevents the onset or ameliorates the clinical manifestations of autoimmune diseases in rigorous randomized clinical trials.

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