Is Vitamin D a New Therapeutic Agent in Autoinflammatory and Pain Syndromes?

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For decades it has been recognized that vitamin D has a seminal role in the homeostasis of calcium metabolism. However, it has become clear that vitamin D has additional important functions affecting other cells, tissues, and systems [1,2]. Although primarily retrospective, data indicate that vitamin D insufficiency is related to the development of cancer, autoimmune diseases, hypertension, infectious diseases, diabetes, cardiovascular disease, musculoskeletal disorders, and asthma, as well as psychiatric conditions such as schizophrenia, depression and dementia [1,2]. A recent meta-analysis demonstrated that vitamin D supplementation resulted in reduced all-cause mortality [3].

Immune regulation is another recently explored function of vitamin D. In particular, poor vitamin D status has been linked to the development and higher prevalence of various autoimmune disorders including type 1 diabetes mellitus, multiple sclerosis, rheumatoid arthritis, Bechcet's disease, and inflammatory bowel diseases [4]. The active form of vitamin D has been shown to arrest the development of these autoimmune diseases in experimental models [1]. In vitamin D receptor knockout mice, T cells that lack these receptors up-regulate the immune response by excessive secretion of pro-inflammatory cytokines [5]. Vitamin D induces differentiation arrest and maturation of populations of dendritic cells, T cells and B cells, with increased production of interleukin-10 and reduced IL-12, resulting in attenuation of the immune response by suppressing dendritic cell development and inducing apoptosis of inflammatory immune cells. Vitamin D also decreases the concentration of the pro-inflammatory cytokine IL-17. Fewer plasma and post-switch memory B cells are produced. Higher numbers of tolerogenic dendritic cells and natural killer T cells have been reported following exposure to vitamin D, which eventually down-regulates autoimmune activity [6].

Vitamin D may be derived from natural sources, but it is primarily synthesized within the cutaneous tissue by a photochemical reaction enhanced by ultraviolet B rays. Hypovitaminosis D is a worldwide epidemic, due to insufficient intake and inadequate sunlight exposure. Worldwide surveys estimate that between 40 and 90% of older individuals are vitamin D-insufficient [2,7]. Vitamin D deficiency is also highly prevalent in patients with autoimmune disorders, regardless of age, gender or geographic location [8]. Epidemiological data indicate that more than 60% of patients with rheumatoid arthritis have low 25-hydroxyvitamin D levels (< 50 nmol/L) [9]. A recently published survey found an 84% prevalence of vitamin D insufficiency in a population of 850 RA patients. Patients with inadequate vitamin D levels had a higher likelihood (odds ratio 2.00, 95% confidence interval 1.63–2.45) of having anti-cyclic citrullinated peptide antibodies. In that survey, severe deficiency (< 20 ng/ml) was associated with greater numbers of tender joints [10]. Other studies have associated low vitamin D levels with enhanced disease activity in systemic lupus erythematosus [10-12].

IL = interleukin
RA = rheumatoid arthritis

Heidari et al. [13] recently compared serum vitamin D levels in 276 patients with non-specific skeletal pain diagnosed variably as leg pain, widespread pain, arthralgia, rib pain, back pain, and fibromyalgia, to levels in 202 matched controls. They reported significantly higher rates of vitamin D deficiency in the patients compared to controls (63.4% vs. 36.1%, respectively, $P < 0.0001$). A systematic review by Straube et al. [14] of 22 studies indicated a strong association between vitamin D deficiency and chronic pain.

It has previously been suggested that vitamin D therapy might be effective for patients with inflammatory and non-inflammatory rheumatic diseases. Interestingly, not many studies have considered vitamin D supplementation as a therapeutic option for rheumatic conditions. One small open-label intervention study demonstrated a reduction in disease activity following 12 weeks of treatment with 2 μg/day of 1,25(OH)2D in patients with established RA [15]. In another uncontrolled trial, 20 people with RA were given a 1 μg dose for only 2 months; no improvement was noticed in disease scores [16]. There is a definite lack of studies on vitamin D supplementation through controlled sunlight exposure for patients with chronic inflammatory or pain conditions.

In the current journal, Harari et al. [17] investigated whether vitamin D supplementation led to decreased pain and disease activity in 60 Norwegian

patients who arrived at a Dead Sea resort area for 21 days of medical rehabilitation. The patients suffered from chronic pain syndromes, RA, and osteoarthritis. All patients were exposed to the sun under medical supervision. After 3 weeks of treatment, 25(OH)D serum levels increased significantly from an average of 71.3 ± 26.6 nmol/L at arrival to 89.3 ± 23.2 nmol/L prior to departure. The increased levels were associated with decreased musculoskeletal pain and disease severity. This study is limited by the small study group and the fact that the researchers did not use validated disease activity measures to assess disease severity.

The fact that such a high percentage of Norwegian patients had deficient vitamin D serum concentrations is not surprising. It has been recognized that latitude is a significant determinant of UV exposure and vitamin D production [18,19]. Vitamin D deficiency is not confined to Northern climates or to dark-skinned populations. Low ambient temperatures during the winter season, cloud cover, cultural or religious norms, and risk of skin cancer prevent many individuals from sufficient sunlight exposure. In the December 2010 issue of this journal, Oren and co-workers [20] presented a study assessing the status of vitamin D in Israel. They reported that although Israel is situated in a coastal area and is characterized mostly by sunny year-round weather, vitamin D deficiency is prevalent. In their study, 78% of the 195 subjects who participated had insufficient vitamin D serum concentrations (below 75 nmol/L), and 27% of these were also vitamin D-deficient (below 37.5 nmol/L). They found that in Israel, vitamin D insufficiency is widespread across all ages and ethnic groups, genders, and seasons of the year.

In clinical practice, the etiology of skeletal pain remains unknown in a substantial proportion of our patients who present with skeletal pain as their chief complaint. Recent observations, including those of Harari et al. [17], suggest a rationale to evaluate the association between vitamin D deficiency and non-specific musculoskeletal pain. Randomized controlled trials are still needed to establish whether correction of vitamin D insufficiency confers additional benefits in the prevention and treatment of autoimmune rheumatic diseases. It is also uncertain if there is any clinical benefit in vitamin D supplementation for patients with autoinflammatory conditions who have adequate serum vitamin D levels.

25(OH)D = 25-hydroxyvitamin D

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"A faith is a necessity to a man. Woe to him who believes in nothing"

Victor Hugo (1802-1885), French poet, playwright, novelist, essayist, visual artist, statesman, human rights activist and exponent of the Romantic movement in France. His most well-known works are Les *Misérables* and *The Hunchback of Notre-Dame*

"An eye for an eye only ends up making the whole world blind"

Mohandas Gandhi (1869-1948), political and ideological leader of India who advocated civil disobedience and non-violence in the struggle for independence from British rule