The Diverse World of Vitamin D: Does It Also Modulate Pain Sensation?

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KEY WORDS: fibromyalgia, pain, vitamin D, cancer, autoimmunity

IMAJ 2009;11:371–372

It has become widely accepted that vitamin D is an essential nutrient for many tissues and is involved in numerous biological processes beyond bone metabolism. Many tissues express the 1α-hydroxylase enzyme enabling the conversion of circulating 25-hydroxyvitamin D to 1,25(OH)2D, which consequently affects various autocrine and paracrine biological processes [1]. Directly or indirectly, 1,25-dihydroxyvitamin D has been shown to take part in the regulation of more than 200 genes responsible for cellular proliferation, differentiation, apoptosis and angiogenesis [1-3].

Humans obtain vitamin D from two main sources; the first is via dietary intake from ordinary food or supplements [4] and the second is the product of the action of sunlight and particularly ultraviolet B radiation (wavelength 290–315 nm) that penetrates the skin and converts 7-dehydrocholesterol to previtamin D_3, which is further converted to vitamin D_3 [5].. Nutritionally, vitamin D is rarely obtained in ordinary diets in sufficient amounts. It is abundant in cod liver oil, but other sources such as other fish oil, egg yolk or liver do not supply the daily requirements that are estimated as 400–600 international units. Furthermore, many clinicians believe that the proper daily requirement exceeds these recommendations and is around 2000–4000 units [6]. Interestingly, the total daily requirements can be provided by exposure to sunlight; a single sunbath in the summer for a fair-skinned individual may produce 20,000 units of vitamin D, an amount equivalent to 200 glasses of milk [6]. However, activities of modern life take place mostly indoors, impeding adequate sunlight exposure and, consequently, vitamin D synthesis.

Numerous cells such as neurons, prostatic, breast and gastrointestinal cells as well as various immune cells have vitamin D receptors and respond to 1,25-dihydroxyvitamin D [1,2,4,7]. Interestingly, vitamin D was shown to decrease cellular proliferation of both normal cells and cancerous cells and to restrain overactive immune cells. These *in vitro* findings were found to have clinical correlates; lower serum vitamin D concentrations were associated with higher rates of breast and prostatic cancer. Vitamin D deficiency was also found at higher rates in patients with various autoimmune conditions such as multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis and others [1,8]. Recently, low levels of 25-hydroxyvitamin D were found to be associated with a higher risk of myocardial infarction in men even after controlling for classical coronary disease risk factors [9].

A recent metaanalysis noted reduced all-cause mortality with vitamin D supplementation [10]. This observation contrasts with the lack of efficacy witnessed with other widely used vitamins such as the antioxidant vitamins A and E, where a possible increment of overall mortality rates with their supplementation was noted [11].

Several reports suggested that vitamin D may have a role in chronic widespread pain syndromes. Yet no clear biological mechanism has identified the manner by which vitamin D deficiency or supplementation enhances or prevents pain respectively.

Fibromyalgia is a well-known yet ill-defined chronic pain syndrome. Wolfe et al. [12] found it to be 10 times more common in females, with a rising prevalence from 2% at age 20 to 8% at age 70 [12]. Experiencing diffuse and persistent pain, which fits the American College of Rheumatology criteria for fibromyalgia, occurs in many other medical conditions, such as migraine, chronic fatigue pain, myofascial pain and irritable bowel syndrome, rendering the accurate diagnosis of these conditions troublesome. Several attempts have been made to link fibromyalgia syndrome with vitamin D deficiency. Huisman and co-authors [13] showed in a cross-sectional study that 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D and parathyroid hormone levels in 25 Caucasian patients with SLE and 25 fibromyalgia female patients were similar; both groups were found to be vitamin D deficient. Reports dealing with chronic pain as a primary complaint detected conflicting evidence regarding vitamin D status or

SLE = systemic lupus erythematosus

supplementation [14,15]. In the current issue of *IMAJ*, Tandeter et al. [16] report that the serum levels of vitamin D in fibromyalgia patients were equal to those in a matched control group. In a logistic regression analysis they failed to show that serum vitamin D levels in their cohort had any predictive value with regard to having or not having fibromyalgia. They made no attempt to assess any linkage between the severity of fibromyalgia and the corresponding vitamin D serum concentrations.

Recently Straube et al. [17] conducted a critical analysis on this issue; they identified three observational studies exploring differences in 25-OH vitamin D levels between patients with and without chronic musculoskeletal widespread pain. Two very small studies (104 patients in total) [18,19] claimed significantly reduced 25-OH vitamin D levels in patients with pain compared to controls. However, in a recent large study [20], a significant association between 25-OH vitamin D levels and increased pain was found in only one of the several analyses for 3495 women but not for 3365 men.

Interventional studies dealing with vitamin D supplementation were found to be highly biased. In their review Straube and co-workers [17] cited treatment studies involving 733 patients; 229 of them were included in randomized double-blind trials, of whom only 22 (10%) showed a significant improvement in pain measures with vitamin D. In contrast, six of eight treatment studies that were not double blind showed significant relief of pain following vitamin D administration (457 of 504 patients, 93%). Interestingly, in most of the trials serum concentrations of vitamin D were not measured despite supplementation with the vitamin, hence no clear cause-effect relationship could be determined.

Despite the impressive knowledge that is accumulating today about vitamin D and its effects on multiple biological pathways, there is no substantial evidence to support its role in pain mediation and perception. Further studies dealing with higher doses of vitamin D supplementation and perhaps more valid and accurate clinical assessments are therefore warranted before any linkage between vitamin D and fibromyalgia can be drawn.

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