

Is there a role for vitamin D in the treatment of chronic pain?

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Abstract: Chronic pain is highly prevalent in the developed world, and levels of vitamin D are often lower among those with chronic pain conditions than those without. Supplementation of vitamin D has been investigated as a potential independent treatment for chronic pain. This paper presents an overview of the scientific evidence and provides recommendations for use of vitamin D in clinical practice with chronic pain patients.

Keywords: chronic pain, supplementation, treatment, vitamin D

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Introduction

We have addressed the question of the role of vitamin D in chronic pain based on a literature search which included the key terms chronic pain, musculoskeletal pain, vitamin D, vitamin D deficiency, treatment, supplementation, trials, and epidemiology. Relevant articles were identified in *PubMed*, *Google Scholar* and *Cochrane* databases and supplemented by manual searches, including hand searching of key journals and references from identified articles. All searches were conducted up to the end of June 2016.

Chronic pain

Chronic pain is defined as ‘pain persisting beyond normal tissue healing time (i.e. 3 months)’.¹ As a number of conditions generally fall under this broad category, including back pain, migraines and osteoarthritis, chronic pain is relatively common. Prevalence estimates from developed countries are around 20%, but range from 12–44% in the general adult population, more commonly affecting women and older adults.^{2–5} The aetiology of chronic pain is complex and treatment usually requires both a pharmacological and nonpharmacological approach.^{6,7} Moreover, effective treatment for the management or eradication of chronic pain is of high importance, as chronic pain is a leading cause of disability⁸ and has high societal costs.^{9–11}

The importance of Vitamin D

Sources of vitamin D include exposure to sunlight, food intake and dietary supplement.¹² It is transformed by the liver into calcidiol or 25-hydroxyvitamin D [25(OH)D], and circulated throughout the body *via* the blood, where it is then converted by other tissues and the kidney into the hormone calcitriol or 1,25-dihydroxyvitamin D [1,25(OH)₂D].^{13,14} Sufficient levels of circulating vitamin D are necessary for absorption of other essential vitamins and minerals, particularly calcium, which plays a crucial role in promoting good bone and muscle health.¹⁵ Vitamin D also operates to reduce inflammation, modulate cell growth, and influences the immune and neuromuscular systems,¹⁴ and is of great physiological importance.

Insufficient and deficient vitamin D levels have been associated with a multitude of poor health outcomes, including cardiovascular disease, hypertension/blood pressure, type-II diabetes, cancer (e.g. colorectal, breast, prostate), autoimmune diseases (e.g. multiple sclerosis), inflammation, mood disorders/depression, cognitive function and Alzheimer’s, as well as all-cause mortality,^{16–20} although findings from observational studies are largely inconsistent and not always supported by randomized controlled trials.^{19,20} The high prevalence estimates of vitamin D deficiency, 20–50% in studies from North America, Europe and Australasia^{21–27} are

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therefore cause for considerable public health concern.

Prevalence of vitamin D deficiency among chronic pain patients

While general population estimates of deficiency have come from large population studies, evidence of the prevalence of vitamin D deficiency [serum 25(OH)D levels ≤ 50 nmol/l] in rheumatic and chronic pain populations generally come from smaller clinic-based studies. Prevalence of hypovitaminosis D was found to be 86% in a Swiss rheumatology outpatient population.²⁸ Estimates range from as high as 93% among individuals with persistent, nonspecific pain²⁹ and as low as 26% in a sample of chronic pain patients being treated at a pain clinic.³⁰ Among consecutive new patients in a rheumatology clinic, the prevalence of vitamin D deficiency was 70% [serum 25(OH)D ≤ 53 nmol/l] and severe deficiency was 26% [serum 25(OH)D ≤ 25 nmol/l],³¹ with deficiency among Musculoskeletal (MSK) conditions associated with chronic pain as follows: inflammatory joint diseases/connective tissue diseases, 69%; soft tissue rheumatism, 77%; osteoarthritis, 62%; nonspecific musculoskeletal back pain, 75%, and osteoporosis, 71%.³¹ Results from an audit of 25(OH)D in rheumatology outpatients indicate that levels were lower among rheumatology patients when compared with osteoporotic/osteopaenia patients, with the lowest levels found in inflammatory arthritis and fibromyalgia/chronic pain patients overall.³²

Direct associations between vitamin D and chronic pain

Vitamin D deficiency has also been linked to chronic pain. Cross-sectional findings suggest that men with chronic widespread pain (CWP) and 'other pain' had increased odds of lower 25(OH)D levels when compared with those without pain, even after adjusting for age and lifestyle factors.³³ However, identified associations between lower serum 25D concentrations and chronic pain did not remain after adjustment for covariates in the Concord Health and Ageing in Men Project.³⁴ In the 1958 British birth cohort, a cross-sectional association between vitamin D and CWP was only found among women and remained in fully adjusted models.³⁵ Evidence from a case-control study did not find an association between vitamin D

levels and chronic low back pain in a Swedish primary care setting.³⁶ No statistically significant difference in mean levels of serum 25(OH)D was found between cases with fibromyalgia and age/sex-matched controls in Brazil.³⁷ Longitudinal data following men in the European Male Ageing Study suggest that those with low levels of 25(OH)D (<15.6 ng/ml) had nearly two-times greater odds of developing CWP than those with levels ≥ 36.3 ng/ml, yet this relationship did not remain significant after accounting for body mass index (BMI) or depression.³⁸

Mechanisms underlying the relationship between vitamin D and chronic pain

Vitamin D deficiency may negatively contribute towards a chronic pain state. Research suggests that vitamin D may play a vital role in various cellular activities thought to be protective against chronic pain development and modulation. Briefly, vitamin D has been found to act as a neuroactive steroid, interfere with the creation and role of neurotrophins, influence prostaglandin action, effect inflammatory pathways, and inhibit nitric oxide synthase and T-helper cells.^{39,40} Despite a growing body of literature, there is not a definitive understanding of how vitamin D or vitamin D supplementation precisely functions to prevent or ameliorate chronic pain.

Vitamin D supplementation as treatment for chronic pain

Recent systematic reviews and meta-analysis have synthesized evidence from experimental trials using vitamin D therapeutically for the treatment of chronic pain. A 2015 Cochrane review identified ten studies meeting their criteria of double-blind trials of using vitamin D supplementation compared with placebo or active comparators for the treatment of chronic painful conditions.⁴¹ Included studies were found to be methodologically of low quality, as well as heterogeneous, that is, varying by painful chronic condition, dosing of vitamin D, and outcome measures investigated.⁴¹ Findings from other systematic reviews have also reached the same conclusions, that there is moderate level of evidence that vitamin D supplementation was not helpful for treating chronic nonspecific musculoskeletal pain patients⁴² and inconclusive evidence of a definitive positive effect of vitamin D on chronic pain states.⁴³

Current practice on 25(OH)D levels and treatment/maintenance doses of vitamin D in chronic pain

Guidelines for vitamin D levels and the treatment/maintenance doses of dietary vitamin D supplements have not been specifically developed for a chronic pain population. Current practice should therefore rely upon guidelines established for healthy adults and those at risk for vitamin D deficiency.

Serum 25(OH)D is the biomarker recommended to assess vitamin D exposure.¹⁴ For healthy adults, levels of 25(OH)D concentration <30 nmol/l (<12 ng/ml) indicate vitamin D deficiency, whereas 25(OH)D concentrations of 30–50 nmol/l (12–20 ng/ml) suggests insufficiency. Serum 25(OH)D concentrations above 50 nmol/l (>20 ng/ml) are considered sufficient vitamin D levels, however concentrations over >125 nmol/l (50 ng/ml) can be considered harmful.¹⁴

More conservative cutoff points are recommended by some for those at risk for vitamin D deficiency, for example those with malabsorption syndromes (e.g. inflammatory bowel disease, Crohn's disease), taking certain medications (e.g. anticonvulsant medications; steroids), older adults with history of falls/fractures; and obese adults (BMI > 30 kg/m²).¹⁵ For these individuals, levels of 25(OH)D concentration <50 nmol/l (<20 ng/ml) may be considered to indicate vitamin D deficiency, whereas 25(OH)D concentrations of 52.5–72.5 nmol/l (21–29 ng/ml) indicate insufficiency and 25(OH)D concentrations >75 nmol/l (>30 ng/ml) indicate sufficient vitamin D levels.¹⁵

The recommended dietary intakes of vitamin D are 600 IU/d for adults aged 19–70 years and 800 IU/d for adults aged 70+ years, and individuals at risk for vitamin D deficiency are recommended to take at least 1500–2000 IU/d of supplemental vitamin D to raise the 25(OH)D serum concentration above 30 ng/ml.¹⁵ For the UK these recommended intakes are currently under-review by the Scientific Advisory Committee on Nutrition. Individuals at risk for vitamin D deficiency who are obese or taking medications (e.g. anticonvulsants, steroids) are additionally encouraged to take at least two to three times more vitamin D as recommended for their age group, with a tolerable upper intake level of 10,000 IU/d.¹⁵

Recommendations for clinical practice of the treatment of vitamin D deficiency among chronic pain patients

Individuals with chronic pain may be at increased risk of vitamin D deficiency, especially if they are obese, likely to have reduced sun exposure, low levels of physical activity, diets low in vitamin D-rich foods, or malabsorption issues. Anticonvulsants and steroids commonly used to treat chronic pain and rheumatic conditions (e.g. fibromyalgia) can reduce vitamin D levels.^{15,41} Additionally concomitant liver or renal disease may reduce the body's ability to metabolize vitamin D.^{15,41} Although there is no concrete evidence that vitamin D supplementation is an effective treatment for chronic pain, no contraindications for the use of vitamin D supplementation among chronic pain patients exist, as vitamin D poses a low health risk in general, is generally well accepted, and is inexpensive.^{41,44} Appropriate vitamin D supplementation should be recommended where levels are either insufficient or deficient according to the individuals' additional risk factors (e.g. current medications, obesity level, and exposure to sunlight).

Summary

There is no doubt that vitamin D plays a vital physiological role in the human body. While associations between insufficient and deficient levels of vitamin D and poorer health outcomes have been established, the relationship between vitamin D and chronic pain is less well understood. Indeed, no definitive mechanism exists to explain how vitamin D influences chronic pain development. Given the prevalence of vitamin D deficiency in chronic pain patients, supplementation may offer numerous health benefits. However, in light of the current lack of evidence, vitamin D supplementation cannot be considered an efficacious independent treatment for chronic pain at this time.

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