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REVIEW

Vitamin D Deficiency and Pain: Clinical Evidence of Low Levels of Vitamin D and Supplementation in Chronic Pain States

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ABSTRACT

Introduction: A number of studies suggest a link between low levels of 25-hydroxy vitamin D and incidence of acute and chronic pain. Clinical studies of vitamin D supplementation in patients with known vitamin D deficiency have shown mixed results in improving pain scores.

Methods: In this article, vitamin D deficiency risk factors are observed and adequate levels of 25-hydroxy vitamin D defined. Clinical supplementation with vitamin D is explored, including the schedules used in published clinical trials. Evidence of the effectiveness of vitamin D supplementation for the treatment of chronic pain conditions from double-blind randomized controlled trials (RCTs) is examined.

Results: The scientific evidence for vitamin D as a treatment option for chronic pain is limited due to lack of RCTs. It cannot be stated conclusively that vitamin D deficiency is directly linked to the etiology or maintenance of chronic pain states.

Conclusion: There remains a growing body of both clinical and laboratory evidence pointing to a potential relationship between low levels of 25-hydroxy vitamin D and a variety of chronic pain states. More focused research involving large RCTs is necessary.

Keywords: Chronic Pain; Pain Processes; Supplementation; Vitamin D deficiency

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INTRODUCTION

It appears that circulating vitamin D, the parent compound for tissue vitamin D activation, has an important direct physiological role beyond what was originally anticipated through the local tissue autocrine system [1]. A number of studies have suggested a link between low levels of 25-hydroxy vitamin D [25(OH)D] and the incidence of both acute and chronic pain [2–5]. Clinical studies of vitamin D supplementation in patients with known vitamin D deficiency have shown mixed results in improving pain

scores [6]. Vitamin D is cheap and has relatively few adverse effects. Its use in chronic pain could therefore be advocated even if the benefit was of modest size [4]. In general, there is a positive public perception of vitamin supplementation which could result in high rates of adherence [4].

Synthesis, Absorption, and Metabolism of Vitamin D

Chemically, vitamin D is a fat-soluble secosteroid (that is, a steroid in which one of the bonds in the steroid rings is broken). The most common forms are vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol), which are collectively known as calciferol. Although it is called a vitamin, vitamin D is really a hormone. It can be produced endogenously by humans in the skin from a precursor 7-dehydrocholesterol which is converted to vitamin D_3 after exposure to ultraviolet B. Vitamin D can also be obtained from a limited number of dietary sources; vitamin D_2 from plant origins and vitamin D_3 from animal origins. However, few foods have naturally occurring substantial vitamin D_2 and vitamin D_3 levels to make this a significant source of vitamin D in humans.

Vitamin D from the skin and diet is hydroxylated in the liver by one of several cytochrome P450 enzymes to the prehormone 25-hydroxy vitamin D [calcidiol, or 25(OH)D] that is encoded by the gene CYP27A1 [7–9]. Most circulating 25(OH)D and the active form of vitamin D, namely 1,25-dihydroxy-vitamin D [$1,25(OH)_2D_3$], are transported in the blood bound to vitamin D-binding protein (DBP; 80–90%) and to albumin (10–20%); only a small fraction remains free or unbound [10].

However, vitamin D can also be hydroxylated to 25(OH)D in all tissues of the body, achieving autocrine production of 25(OH)D in these tissues [1]. 25(OH)D is then further metabolized in the kidneys and possibly in a wide variety of extra-renal tissues by the enzyme 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) to its active form, namely, 1,25-dihydroxy-vitamin D [$1,25(OH)_2D_3$]. Vitamin D exerts its effects by modulating gene expression after binding to vitamin D receptor (VDR). There appear to be potential genetic polymorphisms in key genes with vitamin D exposure that can influence bioavailability, transport, and distribution in lipid storage pools, metabolism, and action of vitamin D [8].

Chronic Pain

The International Association for the Study of Pain (IASP) defines chronic pain as "pain that has persisted beyond normal tissue healing time". This is taken (in absence of other criteria) to be 3 months [11]. However, some chronic pain disorders are characterized by recurrent short acute episodes and exacerbations such as trigeminal neuralgia and rheumatoid arthritis.

Chronic pain can be produced after tissue damage (or inflammation), nerve damage, and after alteration of normal neural function. Chronic persistent pain leads to chemical, functional, and anatomical changes throughout the nervous system (in the periphery, spinal cord, and brain) [12–14]. In chronic pain states, the nervous system is altered to produce spontaneous pain that arises without any apparent peripheral stimulus as well as a hypersensitivity to peripheral stimuli [15–18]. Pain hypersensitivity potentiates hyperalgesia (the exaggerated and prolonged response to noxious stimulation) and allodynia (pain resulting from a stimulus that is normally non-painful) [19]. Reduced descending inhibition in

the central nervous system results in increased peripheral noxious signals that provide messages to the brain, and result in an increased experience of pain [20].

THE INTERFACE OF VITAMIN D AND CHRONIC PAIN

Research has shown that vitamin D exerts anatomic, hormonal, neurological, and immunological influences on pain manifestation, thereby potentially playing a role in the etiology and maintenance of chronic pain states and associated comorbidities [21–24]. $1,25(OH)_2D_3$ (i.e., calcitriol) is an active vitamin D metabolite. It plays a role in many biological processes, especially in bone metabolism and muscle function, and is mediated by VDRs [25]. Vitamin D supplementation has been found to improve bone density and musculoskeletal symptoms [26]. Vitamin D deficiency causes muscle weakness and pain in children and adults [27, 28]. Low bone density and osteopenia appear to contribute to chronic pain in patients with cystic fibrosis, and are related to low 25(OH)D levels [29, 30].

Low 25(OH)D levels have been found to be related to heightened central sensitivity (particularly augmented pain processing) upon mechanical stimulation in chronic pain patients [31]. Migraine and fibromyalgia represent a central neural hypersensitivity [32, 33]. Activated microglia, astrocytes, and spinal glia release a variety of neuroexcitatory substances (nitric oxide, excitatory amino acids, proinflammatory cytokines, and mediators) that potentially initiate and maintain the neural hypersensitivity state seen in chronic pain states [32]. As a neuroactive steroid, vitamin D can modulate neuronal excitability

including spontaneous regular firing, action potential duration, intrinsic excitability and sensitivity to neurotransmitters (gonadotropin-releasing hormone, opioidergic neurons) as well as to neurotransmitter receptors such as gamma-aminobutyric acid and N-methyl-D-aspartate [34–36]. Vitamin D plays a fundamental role in astrocyte detoxification pathways, and thereby exerts a neuroprotective effect [37]. Vitamin D suppresses tumor necrosis factor alpha (TNFα), macrophage colony-stimulating factor (M-CSF), and inducible nitric oxide synthase in astrocytes and microglia [38]. TNFα has been convincingly implicated at both peripheral and central levels of sensitization [39]. M-CSF is a cytokine that stimulates proliferation, differentiation, and survival of monocytes and macrophages. Macrophages can release many inflammatory mediators, including proinflammatory cytokines, particularly TNFα and interleukin-1 *beta* (IL-1β), nerve growth factor (NGF), nitric oxide (NO), and the prostanoids [40]. By limiting M-CSF, vitamin D has the potential to inhibit pain pathways. The presence of VDR, 1α-hydroxylase, and DBP in the hypothalamus is suggested as the mechanism by which vitamin D deficiency is implicated in the pathophysiology of various primary headache disorders [41]. Vitamin D upregulates the synthesis of neurotrophins such as NGF, neurotrophin 3, and glial cell line-derived neurotrophic factor, whereas neurotrophin 4 is down-regulated [37, 38, 42–44]. Through this system, vitamin D can potentially affect the development of neurons, as well as their maintenance and survival. NGF is a well-established inflammatory mediator and has direct effects on the sensory nerve endings causing hypersensitivity, amplification of sensory input signals, and enhanced innervation of injured tissue [40, 45–47].

Individuals with sickle cell disease may develop chronic pain for a variety of reasons

including vascular occlusive bone infarction, peripheral nerve injury, central pain sensitization, as well as hyperalgesia syndrome from prolonged high-dose opioid use [48].

VITAMIN D DEFICIENCY

General Prevalence of and Risk Factors Associated With Vitamin D Deficiency

There appears to be a worldwide trend towards nutritional vitamin D deficiency that is causing concern [9]. Estimates of vitamin D deficiency vary across the world and within countries themselves. It has been estimated that a wide range (20–100%) of elderly men and women living in the community in the United States, Canada, and Europe are vitamin D deficient [49].

The major cause of vitamin D deficiency is decreased sun exposure that limits the synthesis of vitamin D [49]. This could occur through stringent application of sunscreen, or active avoidance of the sun for presumed health reasons [50]. Women who cover themselves for cultural or religious reasons are at risk of vitamin D deficiency as well [51]. People with naturally dark skin tone appear to require at least three to five times longer sun exposure to make the same amount of vitamin D as a person with a white skin tone [49]. People with dark-colored skin who live far from the equator are at high risk of developing a vitamin D deficiency. However, there is also evidence that dark-skinned people can be at risk even in sunny climate such as Australia [50]. Age, gender, and race can be factors associated with risk of vitamin D deficiency. In the United States, serum levels of 25(OH)D (nmol/L) among 15,390 adult participants more than or equal to 18 years of age were evaluated [52]. White men and women (83.0 and 76.0 nmol/L, respectively) had higher mean serum levels of 25(OH)D than Hispanic men and women (68.3 nmol/L and 56.7 nmol/L, respectively; $P < 0.0001$), and had higher mean serum levels of 25(OH)D than black men and women (52.2 and 45.3 nmol/L, respectively; $P < 0.0001$) as well. The prevalence of both mild to moderate and severe deficiency of 25(OH)D was higher among women ($P < 0.0001$) and in minority populations ($P < 0.0001$). However, even amongst white men, 34% were found to have low 25(OH)D levels [52].

The elderly are particularly at risk as the body's ability to synthesize vitamin D in the skin decreases with aging [21]. Being less mobile and often confined indoors, their exposure to sunlight can be limited. This applies particularly to institutionalized individuals [50, 53]. Despite the sunny climate in Australia, in a large sample of women in residential care in three of the states, mean 25(OH)D serum levels fell below 50, and below 31.4 nmol/L if they were in high-level care [54]. Neonates may be deficient due to low serum maternal 25(OH)D levels caused by multiparity and by dark maternal skin with restricted sun exposure [50]. Exclusively breast-fed infants, particularly if dark skinned with little exposure to sunlight, are at risk as well [55].

Patients with malabsorption syndromes such as cystic fibrosis, cholestatic liver disease, chronic inflammatory bowel disease (Crohn's disease), or a short bowel syndrome are at risk of developing vitamin D deficiency through limited absorption of dietary vitamin D [50, 56]. Vegetarians may also be at risk of dietary vitamin D deficiency [50]. Obesity is associated with vitamin D deficiency in both adults and children [57–60]. This could be related to increased storage of vitamin D in adipose tissue, limited sun exposure due to increased clothing and immobility, or due to the fact that low vitamin D levels cause parathyroid hormone (PTH) excess and calcium influx into

adipocytes, promoting weight gain [61]. However, it is not known whether adipose tissue merely sequesters vitamin D and its metabolites or whether it functions as a storage pool from which vitamin D and its metabolites can be mobilized [8].

People taking anticonvulsants, glucocorticoids, rifampicin, or highly active antiretroviral drugs are at higher risk of developing vitamin D insufficiency [49, 50]. These drugs enhance the catabolism of 25(OH)D and of 1,25(OH)$_2$D$_3$ [49, 50].

Defining Adequate of Vitamin D Levels

At present, assessment of serum 25(OH)D provides the best measure of vitamin D repletion in humans, reflecting exposure to dietary or endogenous sources of vitamin D as well as indicating other processes such as absorption and metabolism [8, 10, 62]. One functional definition of the optimal vitamin D status is the 25(OH)D levels that maximally suppress PTH [63, 64]; the reason for this is that the major stimulus for PTH secretion is a low level of serum calcium [7, 65]. It is generally agreed that the levels of PTH will start to rise significantly once the serum 25(OH)D levels drops below 75 nmol/L [50]. Many vitamin D scientists advise that the minimum serum 25(OH)D levels should be 75 nmol/L [9, 49, 66]. Most experts now define frank vitamin D deficiency as a serum 25(OH)D level of less than 50 nmol/L [49, 50, 65, 67]. Serum levels between 50 and 75 nmol/L are considered to represent vitamin D insufficiency [9].

Clinical Supplementation with Vitamin D

Vitamin D supplementation increases 25(OH)D serum levels and can therefore potentially correct the effects of vitamin D deficiency [4]. The impact of dietary intake on vitamin D metabolism and the reversibility of chronic pain with normalization of serum 25(OH)D levels remain unclear at present. Variation in vitamin D dosing schedules could have a profound effect in the outcome of clinical trials because of the short circulating half-life of intact vitamin D [1]. The cellular accessibility of the parent compound vitamin D, as well as that of 25(OH)D, is important when considering supplementing with vitamin D in a clinical trial. 25(OH)D and vitamin D can be internalized by cells through one of two mechanisms. Free 25(OH)D can enter the cell by diffusion across the cell membrane or by the DBP receptor-mediated endocytosis by the coreceptors megalin and cubilin [8]. Most circulating vitamin D and 25(OH)D are transported in the blood bound to DBP. The 25(OH)D is tightly bound to DPB. The amount of DBP and its effect on free versus bound 25(OH)D could inversely affect the free 25(OH)D available for uptake by diffusion into cells [8]. This simple diffusion is primarily controlled by the dissociation constant of the vitamin D compound to the DBP. The amount of DBP could also directly influence the uptake of 25(OH)D via the megalin and cubilin coreceptor system [1].

Selection of dosing regimen, such as whether to give supplements at daily, weekly, monthly, or longer intervals, is important in clinical trials of vitamin D as different regimes could influence the outcomes of such studies. Long-term daily dosing of vitamin D will result in a slow rise in circulating serum 25(OH)D levels that will reach a steady state at 3–6 months [1]. Stable circulating serum levels of both vitamin D and 25(OH)D result from daily dosing schedules, whereas weekly doses result in varying serum levels of circulating vitamin D but stable serum levels of 25(OH)D [68–70]. Acute or large bolus dosing with vitamin D

Table 1 Dosing schedules of vitamin D [68, 71–78]

Dose schedule	Dose range (IU)
Daily	400–4000
Weekly	8400–50,000
Monthly	50,000–120,000
Four-monthly	100,000[a]
Yearly	300,000–600,000

[a] Four-monthly dosing schedule was only mentioned in one research trial

appears to produce a variety of rates of 25(OH)D [1].

A wide variety of schedules have been used in published clinical trials (Table 1 [71–78]). However, clinical research studies have shown that supplementary doses less than 1000 IU per day of vitamin D results in only modest increases in serum levels of 25(OH)D that may be inconsequential for achieving optimal serum levels of 75 nmol/L [79, 80].

There does not appear to be any variation in tolerance or toxicity of vitamin D in terms of the dosing regimen [1]. It has been suggested that optimal benefits from vitamin D supplementation would be achieved through a daily dose of vitamin D to ensure stable circulating serum levels over time [1]. Once-daily dosing appeared to be more effective than monthly or 3-monthly dosing in prevention of respiratory tract infections [81]. However, poor adherence with daily dosing of medications and supplements is widely appreciated [72]. Thus, higher and longer interval dosing is likely to result in better adherence. Weekly dosing would be preferable over monthly due to the 3–4 week half-life of 25(OH)D [72]. In a recent study of patients supplemented with either 1200 IU daily or 50,000 IU weekly of vitamin D for 3 months, the serum 25(OH)D level improved in both groups by almost 40%, but the

difference in improvement was not statistically significant between the subgroups [82]. Four-monthly vitamin D supplementation has also been shown to result in positive functional outcomes [78].

Studies have shown that time to equilibrium for vitamin D supplementation is generally 3 to 6 months [83–87].

Vitamin D has relatively few (and usually mild) adverse effects. Excessive inputs of vitamin D potentially produce hypercalcemia, renal stones, and renal calcification, with kidney failure and death. Extremely high serum levels of either 25(OH)D or of vitamin D can result in hypercalcemia via two mechanisms. Firstly, by directly causing high intestinal calcium absorption and bone resorption that is in excess of the kidney's ability to handle the calcemic load. Secondly, by causing displacement of the active form of the vitamin from circulating DBP by high levels of 25(OH)D, resulting in an elevation of free $1,25(OH)_2D_3$ [88]. It appears that the daily intake of vitamin D necessary to achieve serum levels of 75–110 nmol/L is not associated with these risks. Excessive vitamin D intake (over 50,000 IU per day) is rarely associated with hypercalcemia [21]. Doses of 10,000 IU of vitamin D_3 per day for up to 5 months have not been found to cause toxicity [89].

EVIDENCE FROM RECENT RANDOMIZED PLACEBO-CONTROLLED TRIALS OF VITAMIN D SUPPLEMENTATION IN PATIENTS WITH CHRONIC PAIN

There are limited randomized double-blind placebo-controlled trials of vitamin D supplementation to determine the efficacy of

Table 2 Randomized controlled trials on supplementation with vitamin D in chronic pain

References	Condition or population	Patient characteristics (total number, sex, age), and treatment protocol	Aim of study and measurement of outcomes	Study duration	Pain outcomes	Improvement with vitamin D	Oxford grading and limitations of study
Warner and Arnspiger [91]; double-blind RCT	Diffuse musculoskeletal pain and 25(OH)D levels between 9 and 20 ng/ml	50 participants, mean age 56.2 ± 9.3 years, 100% female. Participants were divided into 2 equal groups and were either supplemented with 50,000 IU ergocalciferol per week ($n = 25$) or placebo ($n = 25$). Vitamin D and placebo capsules (identical in appearance) were dispensed in identically appearing capsules	The aim of the study was to evaluate the effect of treatment with vitamin D on musculoskeletal pain. Outcomes assessed were pain measured by VAS and FPS	3 months	There was no difference in the change in VAS and FPS from baseline to 3-month follow-up between the placebo and active TGs. There was no correlation between vitamin D level and pain on VAS (r 0.038) or FPS (r 0.293) at 3-month follow-up. At 3 months, the mean vitamin D level in the active TG was significantly higher than placebo (31.2 ± 6.1 vs. 19.3 ± 6.5 ng/mL, $P < 0.001$)	No	Oxford rating 5/5. Generally this was a high-quality study. It is possible that a therapeutic effect of pharmacologic doses of vitamin D was missed because of (a) the small size of the study; and (b) the normalization of vitamin D levels in 50% of the placebo group (presumably because the study took place during the warm months of the year)
Di Munno et al. [96]; double-blind RCT	Polymyalgia rheumatica of recent onset receiving 6-methylprednisolone	24 participants, mean age 67.9 years (range 51–82 years), 63% (15) female. Participants were divided into 2 equal groups and were either supplemented with 35 μg 25(OH)D₃ per day ($n = 12$) or placebo ($n = 12$) for 25 days per month (monthly equivalent 35,000 IU). All participants received 500 mg calcium per day	The aim of the study was to demonstrate that in patients with polymyalgia rheumatica, possible further bone loss (induced by moderate doses of steroids) could be avoided by administration of 25(OH)D₃ and calcium supplements. Pain on movement and subjective tenderness on palpation of affected areas were evaluated	9 months	Subjective pain on movement (scale 0–4): significantly decreased in both groups over time, but there was no great difference between the groups	No	Oxford rating 2/5. Small number of participants in the study, and no statistics were given for between-groups comparison. The level of vitamin D was not measured during the study

Table 2 continued

References	Condition or population	Patient characteristics (total number, sex, age), and treatment protocol	Aim of study and measurement of outcomes	Study duration	Pain outcomes	Improvement with vitamin D	Oxford grading and limitations of study
Wepner et al. [97]; double-blind RCT	Severe pain from FMS	27 women and 3 men, who fulfilled the 2010 American College of Rheumatology criteria for FMS, with serum calcifediol levels below 80 nmol/L (32 ng/mL), were included and randomized to TG ($n = 15$) or CG ($n = 15$). The goal was to achieve serum calcifediol levels between 32 and 48 ng/mL for 20 weeks via oral supplementation with cholecalciferol. The CG received placebo medication. Depending on their serum calcifediol levels, the TG received 2400 IU (serum calcifediol levels <60 nmol/L) or 1200 IU (serum calcifediol levels 60–80 nmol/L) of cholecalciferol (vitamin D₃) daily, dissolved in a triglyceride solution. The CG received the triglyceride solution without the cholecalciferol	The aims of the study were to establish the role of vitamin D in patients with FMS, and to determine whether serum calcifediol levels within the normal range could improve symptoms, particularly reduce pain, in patients with initially low calcifediol levels (vitamin D deficiency). Pain levels were measured using a VAS scale. Additional variables were evaluated using the SF-36, the Hospital Anxiety and Depression Scale, the FIQ, and the Somatization subscale of Symptom Checklist-90-Revised	Initial supplementation for 20 weeks. Re-evaluation was performed in both groups after further 24 weeks without cholecalciferol supplementation	A marked reduction in pain was noted over the treatment period in the TG. Variance analysis of the 2 groups at 4 time points showed a significant group effect in VAS scores. This also was correlated with scores on the physical role functioning scale of the SF-36. Optimization of calcifediol levels in FMS had a positive effect on the perception of pain	Yes	Oxford rating 5/5. A major limitation of the present study was the small number of participants and the highly selected patient population. Results cannot be therefore extrapolated to patients with chronic pain

Table 2 continued

References	Condition or population	Patient characteristics (total number, sex, age), and treatment protocol	Aim of study and measurement of outcomes	Study duration	Pain outcomes	Improvement with vitamin D	Oxford grading and limitations of study
McAlindon et al. [93]; double-blind RCT	Symptomatic knee OA pain	146 participants with symptomatic knee OA, mean age 62.4 years (SD, 8.5 years); 57 (61%) women, 115 (79%) white race. Participants were randomized to receive either placebo or oral cholecalciferol, 2000 IU daily, with dose escalation to elevate serum levels to more than 36 ng/mL	Primary outcomes were knee pain severity (WOMAC pain scale, 0–20: 0, no pain; 20, extreme pain), and cartilage volume loss measured by magnetic resonance imaging. Secondary end points included physical function, knee function (WOMAC function scale, 0–68: 0, no difficulty; 68, extreme difficulty), cartilage thickness, bone marrow lesions, and radiographic joint space width	Vitamin D supplementation for 2 years. Assessments occurred at a baseline visit, and at months 2, 4, 8, 12, 16, 20, and 24	85% of participants completed the study. Serum 25(OH)D levels increased by a mean 16.1 ng/mL (95% CI, 13.7–18.6) in the TG, and by a mean 2.1 ng/mL (95% CI, 0.5–3.7) in the placebo group ($P < 0.001$). Baseline knee pain was slightly worse in the TG (mean, 6.9; 95% CI, 6.0–7.7) than in the placebo group (mean, 5.8; 95% CI, 5.0–6.6; $P = 0.08$). Baseline knee function was significantly worse in the TG (mean, 22.7; 95% CI, 19.8–25.6) than in the placebo group (mean, 18.5; 95% CI, 15.8–21.2; $P = 0.04$). Knee pain decreased in both groups by a mean −2.31 (95% CI, −3.24 to −1.38) in the TG and −1.46 (95% CI, −2.33 to −0.60) in placebo group, with no significant differences at any time. The percentage of cartilage volume decreased by the same extent in both groups (mean, −4.30 [95% CI, −5.48 to −3.12] vs. mean, −4.25 [95% CI, −6.12 to −2.39]; $P = 0.96$). There were no differences in any of the secondary clinical end points. Vitamin D supplementation for 2 years at a dose sufficient to elevate 25(OH)D serum levels to more than 36 ng/mL when compared to placebo, did not reduce knee pain or cartilage volume loss in patients with symptomatic knee OA	No	Oxford rating 5/5. Baseline knee pain was slightly worse in the TG. Baseline knee function was significantly worse in the TG. A concern in inferring a negative result is the possibility of type 2 error

Table 2 continued

References	Condition or population	Patient characteristics (total number, sex, age), and treatment protocol	Aim of study and measurement of outcomes	Study duration	Pain outcomes	Improvement with vitamin D	Oxford grading and limitations of study
Rastelli et al. [95]; double-blind RCT	AIMSS/joint pain and bone loss	60 women were enrolled. Patients with early breast cancer and AIMSS were stratified according to their baseline 25(OH)D levels. Stratum A (20–29 ng/mL) received either HDD supplementation (50,000 IU capsules weekly for 8 weeks then monthly for 4 months, or placebo. Stratum B (10–19 ng/ml) received either HDD for 16 weeks and then monthly for 2 months, or placebo	The primary goal of the study was to compare the effectiveness of HDD in patients with breast cancer who develop AIMSS after starting anastrozole. A secondary goal of the study was to assess the efficacy of HDD in protecting bone health in breast cancer patients on anastrozole therapy. AIMSS was assessed by the BPI-SF, the FIQ, and the HAQ-DI at baseline, 2, 4, and 6 months. BMD was measured at baseline and at 6 months. The primary end point of the study was change-from-baseline musculoskeletal pain. The secondary end point was percent change in BMD at 6 months	Assessments occurred at a baseline and at 2, 4, and 6 months	Baseline characteristics were comparable between groups. At 2 months, FIQ pain ($P = 0.0045$), BPI worst pain ($P = 0.04$), BPI average pain ($P = 0.0067$), BPI pain severity ($P = 0.04$), and BPI interference ($P = 0.034$) scores were better in the HDD than placebo group. The positive effect of HDD on AIMSS was stronger across all time points in Stratum B than in Stratum A (FIQ pain, $P = 0.04$; BPI average, $P = 0.03$; BPI severity, $P = 0.03$; BPI interference, $P = 0.04$). BMD at the femoral neck decreased in the placebo and did not change in the HDD group ($P = 0.06$). Weekly HDD improved AIMSS and might have a positive effect on bone health	Yes	Oxford rating 5/5. The positive effect of vitamin D supplementation was not maintained at 4 and 6 months once subjects were switched to 50,000 IU monthly. It was possible that high enough levels of vitamin D were not reached to maximize its therapeutic effect

Table 2 continued

References	Condition or population	Patient characteristics (total number, sex, age), and treatment protocol	Aim of study and measurement of outcomes	Study duration	Pain outcomes	Improvement with vitamin D	Oxford grading and limitations of study
Sakalli et al. [98]; double-blind RCT	Pain in the elderly	Community-dwelling elderly subjects of 149 consecutive men and women over 65 years of age were included in the study. 29 were excluded because of contraindications or already receiving vitamin D intake. The remaining 120 cases were given 300,000 IU vitamin D via p.o. and parenteral routes and assessed after 4 weeks. Mean age of all participants was 70.1 ± 4.3 years and there were 57 female participants. There was no difference in age and gender between the groups ($P > 0.05$). The 120 cases were included and randomized into four groups, each containing 30 cases: 1st group took i.m. vitamin D; 2nd group took i.m. placebo; 3rd group took p.o. vitamin D; and 4th group took p.o. placebo	The aim of this study was to investigate the benefits of a single dose per os or parenterally administered vitamin D on increasing the quality of life and functional mobility, and decreasing the pain in the elderly. The serum creatinine, calcium, phosphorous, ALT, ALP, 24-h urine calcium excretion, PTH, and vitamin D levels, as well as VAS for pain assessment, functional mobility with TUG and quality of life with SF-36 before and after the treatment were evaluated	Baseline measurements and assessed after 4 weeks	After treatment, the PTH level of first group was decreased ($P = 0.0001$) and vitamin D level increased ($P = 0.0001$) significantly. In the third group, the PTH level of first group was decreased ($P = 0.0001$) and the vitamin D level increased ($P = 0.004$) and the 24-h calcium excretion in urine ($P = 0.015$) increased significantly. When the pain, the functional mobility, and the quality of life were evaluated, in the first group, the TUG ($P = 0.0001$) and the VAS ($P = 0.0001$) decreased significantly, whereas the SF-36 subtitles increased significantly: physical functioning ($P = 0.0001$), role physical ($P -0.006$), bodily pain ($P = 0.0001$), general health ($P = 0.007$), social functioning ($P = 0.05$), and mental health ($P = 0.048$). In group two, the VAS ($P = 0.001$) decreased significantly; the role physical ($P = 0.009$), and role emotional ($P = 0.034$) increased significantly. In group three, the TUG ($P = 0.0001$) and the VAS ($P = 0.002$) decreased significantly, whereas the physical function ($P = 0.0001$) and role physical ($P = 0.001$) increased significantly. In group four, the VAS ($P = 0.007$) decreased significantly. Megadose vitamin D administration increases quality of life, decreases pain, and improves functional mobility when given via oral or intramuscular routes in the elderly	Yes	Oxford rating 3/5. The study did not describe how the study was double blind. The authors did not state the final number of participants in each group, but merely indicated that if participants did not attend the 2nd examination, they were excluded from the group. This could constitute a fair risk of bias. A major limitation of the study was the small number of participants and the short study duration. The total time spent under sun exposure could not be exactly recorded

Table 2 continued

References	Condition or population	Patient characteristics (total number, sex, age), and treatment protocol	Aim of study and measurement of outcomes	Study duration	Pain outcomes	Improvement with vitamin D	Oxford grading and limitations of study
Schreuder et al. [92]; semi-crossover double-blind RCT	Nonspecific musculoskeletal pain	84 non-Western immigrants were enrolled in the study, of which 64 were female. At baseline, patients were randomized to placebo or to vitamin D (150,000 IU vitamin D_3 p.o.). At week 6, patients in the original vitamin D group were randomized a second time to receive vitamin D (again) or switched to placebo, whereas patients in the original placebo group were all switched to vitamin D	The main outcome was self-assessed change in pain and function after the first 6 weeks. Patients rated their pain levels in 4 areas of the body on questionnaires using a VAS (range, 0–100) and localized pain by marking a mannequin. At both week 6 and week 12, patients were asked about improvement or deterioration (compared with baseline) of their pain on a 5-point Likert scale, and about adverse effects. Self-reported improvement in ability to walk stairs at week 6 and week 12 was also assessed. Levels of 25(OH)D in serum were measured at baseline, and after 12 weeks	Baseline measurements and assessed after 6 weeks.	Patients in vitamin D group were significantly more likely than their counterparts in the placebo group to report pain relief 6 weeks after treatment (34.9 vs. 19.5%, $P = 0.04$). The former were also more likely to report an improved ability to walk stairs (21.0 vs. 8.4%, $P = 0.008$). Pain pattern was not correlated with the success of treatment. There was a small positive effect 6 weeks after high-dose vitamin D_3 on persistent nonspecific musculoskeletal pain. In a non-significant trend, patients receiving vitamin D over 12 weeks were more likely to have an improvement than patients receiving it over 6 weeks	Yes	Oxford rating 5/5. Some limitations of the study were due to the type of intervention. Firstly, a single mega dose of vitamin D enabled maximal patient compliance, but duration of treatment might have been too short. Secondly, the heterogeneity of the enrolled patients might have played a role. A third limitation was lack of data concerning PTH. In the multivariate model, the power to assess multiple determinants was limited by the study size

Table 2 continued

References	Condition or population	Patient characteristics (total number, sex, age), and treatment protocol	Aim of study and measurement of outcomes	Study duration	Pain outcomes	Improvement with vitamin D	Oxford grading and limitations of study
Sanghi et al. [94]; double-blind pilot RCT	Patients with knee OA or OA (with vitamin D insufficiency [25(OH)D ≤50 nmol/L]	106 patients entered study (*n* = 53 in TG, *n* = 53 in placebo). 66 were women ranging in age from 40–74 years (mean 54.11 years). At baseline, the two groups were comparable. Anthropometric measurements, clinical assessment (height, BMI, WOMAC, and VAS), pill counts, and completion of questionnaires were recorded at all visits. Biochemical (blood) assessments were performed at 6 and 12 months. Patients were randomized to receive oral vitamin D or placebo. The TG received oral vitamin D 60,000 IU per day followed by vitamin D 60,000 IU once a month for 12 months	The primary outcome measures were pain and function. The secondary outcome measures were biochemical markers. Clinical symptoms related to knee OA were assessed with the WOMAC index (which assesses pain, stiffness, function, and interpretation response in terms of a 5-point scale). Knee pain also was assessed using the VAS	The patients were followed for 1 year with 5 follow-up visits.	At 12 months, knee pain had decreased in the vitamin D group by a mean −0.26 (95% CI, −2.82 to ± 1.43) on VAS, and by a mean −0.55 (95% CI, −0.07 to 1.02) on the WOMAC. In the placebo group, it increased by a mean 0.13 (95% CI, −0.03 to 0.29) on the VAS, and by a mean 1.16 (95% CI, 0.82–1.49) on the WOMAC (effect size = 0.37 and 0.78). Knee function improved in vitamin D group by a mean −1.36 (95% CI, −1.87 to −0.85) over the placebo group with a mean 0.69 (95% CI, −0.03 to 1.41; effect size = 0.06). There were significant biochemical changes in serum levels of total calcium, 25(OH)D and of alkaline phosphatase	Yes	Oxford rating 5/5. The effect sizes observed for pain and function were statistically significant but very small (less than 1 mm on VAS pain and 2 points on WOMAC). The clinical importance of these results is not clear. This was a pilot study of 1 year with relatively small sample size. No absolute differentiation of grade of knee OA was described

25(OH)D 25-hydroxy vitamin D, *AIMSS* aromatase inhibitor-induced musculoskeletal symptoms, *ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *BMD* bone mineral density, *BMI* body mass index, *BPI-SF* Brief Pain Inventory-Short Form, *CG* control group, *FIQ* Fibromyalgia Impact Questionnaire, *FMS* Fibromyalgia syndrome, *FPS* Functional pain score, *HA-DI* Health Assessment Questionnaire-Disability Index, *HDD* high-dose vitamin D₂, *i.m.* intramuscular, *OA* osteoarthritis, *p.o.* per os (orally), *PTH* parathyroid hormone, *RCT* randomized controlled trial, *SF-36* Short Form Health Survey 36, *TG* treatment group, *TUG* timed up and go test, *VAS* visual analog scale, *WOMAC* Western Ontario and McMaster Universities Arthritis Index

vitamin D treatment in chronic pain conditions.

The authors searched MEDLINE (PubMed) using the search terms "vitamin D and pain". Limits in PubMed were set to "Randomized Controlled Trials" (RCTs) and "humans". Full publications in any language were included. The search was conducted on March 11, 2015. Two authors (E. E. S. and E. A. S.) independently reviewed all titles and abstracts identified by the search. Articles were selected for full-text review if inclusion criteria were met, or if either reviewer considered them potentially relevant. Clinical studies were included only if they reported on populations with chronic pain conditions and investigated pain outcomes after vitamin D supplementation. Data were collected regarding study design, chronic pain condition, population group, patient characteristics, mean or median 25(OH)D levels, treatment protocol (including types and doses of vitamin D preparations administered), concurrent other therapy, study duration, aim of the study, and pain outcomes. To be inclusive, chronic pain was defined in the broadest possible terms. An improvement of chronic pain with vitamin D treatment was defined as a statistically significant improvement compared to placebo. Pooled analysis was not undertaken due to the paucity and the heterogeneity of data. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

The search identified 86 entries. Studies were included if they were double-blind RCTs of vitamin D supplementation compared to placebo in the treatment of chronic pain conditions.

Eight RCTs met these inclusion criteria. Seventy-eight studies were excluded based on the following criteria, namely: pain not measured as an outcome ($n = 25$); acute pain instead of chronic pain ($n = 4$); study was singly blinded or not specifically described as double blinded ($n = 6$); study design only ($n = 1$); not all participants had chronic pain ($n = 1$); there was no supplementation with vitamin D ($n = 4$); and the study did not control for vitamin D independent of other treatments ($n = 37$). Only one reason for exclusion was stated. However, some studies may have had more than one reason for exclusion (see Table S1 in the electronic supplementary material for details). The 8 data sets ranged in size from 24 to 146 participants. The total number of participants in the "pain" and "control" groups was 620 of which 396 were female. The majority of the studies were of high methodological quality (Oxford Quality Score 5/5) suggesting little likelihood of methodological bias [90].

There were five studies related to musculoskeletal pain [91–95], of which two were of diffuse or generalized musculoskeletal pain [91, 92]. There were three studies of specific musculoskeletal pain, two involving osteoarthritis of the knees and one of aromatase inhibitor-induced musculoskeletal pain [93–95]. There was one study of each of the following: polymyalgia rheumatica [96]; fibromyalgia [97]; and generalized pain of the elderly [98]. Two studies [96, 98] had lower Oxford Quality Scores and were potentially prone to bias.

There were 5 studies, involving 400 participants, which showed a positive correlation between vitamin D supplementation and subjective pain rating. The four other studies (220 participants) showed no change in pain levels after supplementation. The supplementation regime varied widely and the vitamin D treatments involved monthly equivalent doses that varied

from 35,000 to 300,000 IU. Duration of supplementation was from 1 to 24 months.

The results of this search are shown in Table 2 [91–98].

DISCUSSION

Evaluation of clinical studies regarding the use of vitamin D for the treatment of chronic pain was previously undertaken in 2008 [6]. The authors searched MEDLINE (PubMed) using various search terms for vitamin D and pain prior to September 2008. Twenty-two relevant studies were identified that reported mean 25(OH)D levels and/or investigated the results of vitamin D treatment in patients with chronic pain conditions. Only five of these studies were randomized double-blind trials of vitamin D treatment. Vitamin D treatments involved monthly equivalent doses between 1200 and 400,000 IU. Fourteen studies were in musculoskeletal pain, five in chronic widespread pain or fibromyalgia, one in diabetic subjects with neuropathic pain, one addressing an unusual hyperaesthetic pain syndrome, and one in various conditions. Duration of treatment was from a few days to 12 months, although most studies lasted 2 months or more. Treatment studies involved 733 patients. Randomized double-blind trials involved 229 patients, of whom only 22 (10%) were in a trial with a significant improvement in pain with vitamin D, and then only on a pain mobility measure; 207 patients were involved in trials with no significant improvement in pain with vitamin D. There was also no apparent correlation between significant improvement in pain with vitamin D and with a particular preparation, dose, or condition. There was no persuasive evidence of lower levels of 25(OH)D in those with chronic pain than in the control

populations. There was a striking contrast in treatment effects between randomized, double-blind trials that minimized bias and those with designs known to be subject to bias. In the former, only 10% of patients were in trials showing a benefit of vitamin D treatment; in the latter, 93% were in trials showing a benefit of vitamin D treatment [6]. This study highlighted the need for further randomized double-blind placebo-controlled trials.

A Cochrane review of randomized double-blind trials of vitamin D supplementation compared with placebo was published in 2010 [4]. The aim was to determine the efficacy of vitamin D in the treatment of chronic pain conditions. Only four studies (with a total of 294 participants) were included; eleven trials were excluded due to poor methodological design, or because not all participants received a clearly defined chronic pain diagnosis [4]. The studies included were similar in quality, used analogous chronic pain conditions with comparable outcome measures [91, 96, 99, 100]. Patients were supplemented with varying amounts and formulations of vitamin D for periods ranging from 16 weeks to 12 months. In summary, out of the four trials reviewed, the benefit of using vitamin D in chronic pain treatment was only shown in one trial. In the other three trials, there was no significant beneficial effect of vitamin D over placebo. Adverse effects of treatment were infrequent, and occurred at the same rates in vitamin D and placebo groups [96, 100].

Our study concurs with the results of the previous review on the subject published in 2009 and the Cochrane review published in 2010, in that there is insufficient high-quality evidence for a definitive effect of vitamin D in chronic pain. However, a trend appears in a positive direction indicating a beneficial effect of vitamin D over placebo in chronic pain.

The number of randomized placebo-controlled double-blind studies is increasing which is encouraging. Six of the RCTs included in our study were published since 2011. Although the search strategy of this comprehensive review was thorough, it is possible that some randomized clinical trials might not have been located. A positive publication bias cannot be excluded as journals are reluctant to publish negative results. The overall picture generated by a review of this type could thus be a false positive.

CONCLUSION

Studies using visual analog scale (VAS) pain scores as the primary or solitary outcome measure have shown mixed results in chronic pain patients when evaluating the impact of vitamin D supplementation in this condition [82, 91, 101–103]. Significant improvements in assessment of sleep, mood, pain levels, well-being, and various aspects of quality of life with vitamin D supplementation have been shown [82, 104–107]. Whilst there is a growing body of both clinical and laboratory evidence pointing to a potential relationship between low levels of 25(OH)D and chronic pain, it is not possible to state conclusively that vitamin D deficiency is directly linked to the etiology or maintenance of chronic pain states. The scientific evidence for the use of vitamin D as a treatment option for chronic pain is limited at present due to low-quality designs, and due to the lack of RCTs.

A number of questions remain with regard to supplementation of vitamin D in patients with chronic pain. Vitamin D metabolism and action needs to be further elucidated including extra-renal activation and catabolism, distribution and mobilization from body pools, and its interaction with relevant genetic polymorphisms [8]. There remains some debate over the precise definition of vitamin D deficiency or insufficiency based on the serum levels of 25(OH)D. The influence of age and body weight on the variability of the response of serum levels of 25(OH)D to intake needs to be clarified [8]. More focused research is necessary involving larger double-blind RCTs. These need to be stratified by baseline 25(OH)D levels, type of pain, and the use of adequate doses of vitamin D based on serum levels. More research is necessary to determine whether or not the effect of vitamin D supplementation is limited to patients who are vitamin D deficient. The optimal dose and length of time needed for supplementation need to be assessed as well.

ACKNOWLEDGMENTS

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