Vitamin D and pain

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Pain, according to the recent definition of the International Association for the Study of Pain, is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage [1]. Many pathologies, which have pain as their primary clinical expression, contribute significantly to morbidity and mortality on a global scale.

Although there is growing evidence in the literature of a possible relationship between low levels of 25-hydroxy vitamin D [25(OH)D] and different types of acute or chronic pain and how adequate vitamin D supplementation, particularly in patients with a deficiency, can lead to an improvement in pain symptoms, clinical trials conducted for this purpose have provided inconsistent or discordant results, which, from time to time, have been attributed to participant selection, outcome measures, sample size, vitamin D dosage and/or follow-up duration. Nevertheless, the potential mechanisms by which vitamin D might exert analgesic effects remain poorly understood.

Clinical research in the area of the correlation between chronic pain and vitamin D deficiency is limited. There are still very few randomised, controlled, and blinded studies. Regardless, clinical trials have shown that vitamin D is able to exert anatomical and physiological influence on the manifestation of pain, thus playing a positive role in the aetiopathogenesis and maintenance of chronic pain states and associated comorbidities. Manifestations of pain associated with immunological, hormonal, and neuronal changes are potentially influenced by vitamin D levels. Indeed, low vitamin D levels have been found in patients with various pain states such as headache, abdominal pain, knee pain, low back pain, persistent musculoskeletal pain, costochondritis chest pain, *"failed back syndrome"* and fibromyalgia.

EXPERIMENTAL FINDINGS

The interaction between vitamin D and its VDR receptor appears to play a role in improving pain symptoms through the modulation of key genes associated with pain. Some of these pain genes are common to both superficial and visceral nociception, e.g., TRPV1, the toll-like receptor, trophic factors such as NGF, GDNF and EGFR (Table I). Furthermore, the hypothesis that vitamin D may influence pain signalling pathways is biologically plausible because the gene expression of vitamin D and/or of its VDR receptor, has been demonstrated in the skin (transduction of pain signalling), in the dorsal root ganglion (DRG) neurons (conduction), in the spinal cord (transmission/modulation) and in the brain (pain perception) (Figure 1). The expression of the Vitamin D receptor has been reported in peripheral and central neurons involved in pain sensing and processing. Expression of transcription for the nuclear vitamin D receptor and/or enzymes regulating the active form of vitamin D levels have been demonstrated in the nerve fibres of DRG neurons terminating in the skin, in neurons of the spinal cord and of the brain. The level of VDR transcription in DRG neurons is higher than in other regions of the nervous system. Vitamin D activity is determined by two enzymes, CYP27B1, which activates vitamin D in the kidney and CYP24A1, which inactivates active vitamin D. These two enzymes, together with VDR, are also expressed in nociceptor neurons and in the brain [2].

TABLE I.
Role of trophic factors, influenced by vitamin D, in the pathogenesis of pain.

Trophic factor	Role
Nerve Growth Factor (NGF)	Development of nociceptor neurons and pain processing
Glial cell line-derived neurotrophic factor (GDNF)	Survival and activity of large cutaneous sensory and proprioceptive neurons
Epidermal Growth Factor (EGFR)	Hub or main relay in pain processing and detection

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Conflict of interest
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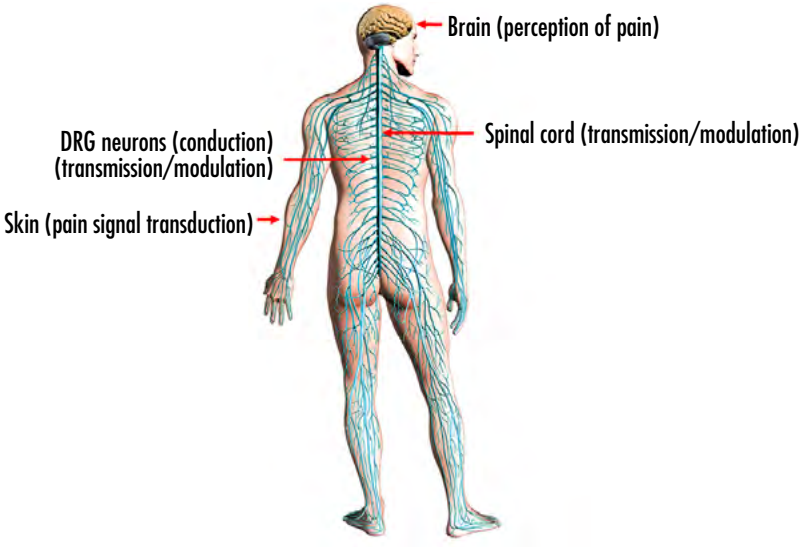

FIGURE 1.
Action of vitamin D on pain transmission pathways.

Vitamin D and VDR play a role in pain signal transduction. Vitamin D interacts with the nerve endings of the nociceptive neurons in the skin to directly detect painful proinflammatory stimuli and to control the activity of the TRPV1 channel in T lymphocytes. The VDR could play a role in modulating the expression of pain genes, e.g., those involved in the development of neurons and Schwann cells, and ion channels expressed in nociceptive neurons that innervate the skin as well. Alterations in the expression or function of vitamin D regulating enzymes, VDR expression, VDR targets on the skin and/or on sensory neurons or associated glial cells could probably have an impact on chronic pain conditions such as neuropathic pain and painful diabetic neuropathy [3].

The interaction between vitamin D and Nerve Growth Factor (NGF) influences nociceptive signal processing. Vitamin D increases the expression of NGF in the DRG neurons innervating the skin in rats, as it does in hippocampal neurons. NGF is a neurotrophic factor necessary for the development and maturation of nociceptors. Under pathological conditions, it appears that NGF levels increase in response to inflammation. In addition, NGF stimulates the release of calcitonin gene-related peptide (CGRP) from peripheral DRG neuron endings. It is believed that CGRP promotes and maintains nociceptive neurons sensitised, which also implies its role in chronic pain. Sensitisation is also enhanced by NGF-facilitated augmented insertion of TRPV1, an ion channel involved in the response to thermal stimulus in the cell membrane. Furthermore, the transcription level of various sodium channel isoforms (e.g., Nav1.6, Nav1.7, Nav1.8 and Nav1.9) is modulated by NGF and ultimately results in increased sodium current density and sensitivity to nociception, mainly by way of Nav1.8. In addition, the development of hyperalgesia during inflammation is believed to stem from an NGF-promoted increase in Nav1.7 expression. It follows that NGF is crucial for the development of nociceptor neurons and for pain processing. Yet, it is still unclear whether this is a direct effect of vitamin D on NGF or if this is an indirect outcome achieved by way of extranuclear or nuclear signalling pathways [4].

Another neurotrophic factor, called Glial cell line-derived neurotrophic factor (GDNF), expressed in a small population of DRG neurons, is implicated in promoting the survival and activity of large cutaneous sensory and proprioceptive neurons. GDNF plays a central role in pain transmission. Recent studies have shown that GDNF and its C-Ret receptor are directly regulated by vitamin D. It could be hypothesised that both vitamin D and its receptor might play a role in sodium channel-mediated neuropathic pain through modulation of GDNF expression. However, experimental verification of this is required [5].

The Epidermal Growth Factor Receptor (EGFR) and its effectors have recently been identified as novel signalling pathways involved in pain processing. It is known that their expression is also regulated by vitamin D. EGFR is widely expressed in cells of the body including in epithelial cells, neurons involved in pain transmission and skin keratinocytes, the latter being a primary source of vitamin D for the body. Though dysregulation of EGFR signalling is believed to underlie the pathogenesis of several cancers, there is also evidence of its role in other pain-causing pathologies as well as in the mechanisms underlying pain detection and processing. EGFR is a key player in pain processing and detection. Since it is already known that EGFR acts as a significant signal hub and relay from a variety of stimuli, its new role in pain signal processing has provided added value to its proposed designation as a "primary hub or relay" for cell signalling. Thus, the inhibition by vitamin D of this important signalling hub, comprising EGFR, could explain its analgesic effects. Actually, several studies have suggested that vitamin D inhibits EGFR gene expression either directly or indirectly [6].

CLINICAL TRIALS (Table II)

Warner et al. evaluated the effect of vitamin D treatment in patients with diffuse musculoskeletal pain and osteoarthritis (controls). Patients with 25-hydroxyvitamin D levels ≥ 20 ng/mL were randomised to receive placebo or 50,000 IU of ergocalciferol once a week for 3 months. Vitamin D treatment had no effect on pain compared to baseline [Visual Analog Scale (VAS) p = 0.73; Functional Pain Score (FPS) p = 0.18] or at 3 months compared to placebo (VAS p = 0.12; FPS p = 0.05, in favour of placebo). The authors concluded that low levels of vitamin D are not associated with widespread musculoskeletal pain and vitamin D treatment does not reduce pain in patients with widespread pain who have low levels of vitamin D [7].

Schreuder et al. studied the effect of high-dose vitamin D_3 on persistent, non-specific musculoskeletal disorders in vitamin D-deficient non-Western immigrants and assessed the correlation between pain type and benefit from the treatment. Patients were randomised to placebo or vitamin D (150,000 IU of oral vitamin D_3). At week 6, patients in the original vitamin D group were randomised a second time to receive vitamin D (again) or to switch to placebo, whilst all the patients in the original placebo group were switched to vitamin D. Patients in the vitamin D group were significantly more likely than the placebo group to report pain relief

TABLE II.
Clinical studies on the use of vitamin D in different painful disorders.

Clinical trial	Condition	Efficacy on pain
Warner AE, 2008 [7]	Musculoskeletal pain	-
Schreuder F, 2012 [8]	Musculoskeletal pain	+
McAlindon T, 2013 [9]	Osteoarthritis of the knee	-
Sanghi D, 2013 [10]	Osteoarthritis of the knee	+
Rastelli AL, 2011 [11]	Breast cancer	+
Wepner F, 2014 [12]	Fibromyalgia	+
Sakalli H, 2012 [13]	Pain in the elderly	+
Gendelman O, 2015 [14]	Musculoskeletal pain	+
Jin X, 2016 [15]	Osteoarthritis	-
Wu Z, 2018 [16]	Pain in the general population	-
Frankling MH, 2021 [17]	Pain in cancer patients	+

six weeks after treatment (34.9% *vs* 19.5%, p = 0.04) and a better ability to climb stairs (21.0% *vs* 8.4%, p = .008). Therefore, 6 weeks after a high dose of vitamin D, a small positive effect was found on persistent non-specific musculoskeletal pain [8].

McAlindon et al., in a study to determine whether vitamin D supplementation reduces symptoms and structural progression of osteoarthritis of the knee, randomised participants to receive placebo or 2,000 IU/day of oral cholecalciferol, with a dose increase to raise serum levels to more than 36 ng/mL. Knee pain decreased in both groups by an average of -2.31 [with 95% confidence interval (CI 95%), -3.24 to -1.38] in the treatment group and by -1.46 (CI 95%, -2.33 to -0.60) in the placebo group, with no significant differences at any time. The percentage of cartilage volume decreased by the same amount in both groups (mean, -4.30; 95% CI, -5.48 to -3.12 vs mean, -4.25; 95% CI, -6.1 2 to -2.39) (p = 0.96). There were no differences in any of the secondary clinical endpoints. In this study, vitamin D supplementation for two years at a dose sufficient to elevate plasma 25-hydroxyvitamin D levels to more than 36 ng/mL, compared to placebo, did not reduce knee pain or cartilage volume loss in patients with symptomatic knee osteoarthritis [9].

Sanghi et al. conducted a study to investigate whether vitamin D treatment could reduce knee pain, improve function, and change the levels of relevant biochemical markers in patients with knee osteoarthritis and vitamin D deficiency. At 12 months, knee pain had decreased in the vitamin D group by an average of -0.26 (95% CI, -2.82 to -1.43) on VAS and -0.55 (95% CI, -0.07 to 1.02) on WOMAC, whilst in the placebo group, it increased by an average of 0.1 3 (95% CI, -0.03 to 0.29) on VAS and 1.16 (95% CI, 0.82 to 1.49) on WOMAC (effect size = 0.37 and 0.78). In the same manner, knee function improved in the vitamin D group by an average of -1.36 (95% CI, -1.87 to -0.85) compared to the placebo group which had an average of 0.69 (95% CI, -0.03 to 1.41; effect size = 0.06). There were significant biochemical changes in serum total calcium, 25(OH)D and alkaline phosphatase. The study results suggest that there is a small, but statistically significant, clinical benefit to vitamin D treatment in patients with knee osteoarthritis [10].

Rastelli et al. conducted a randomised, double-blind, placebo-controlled phase II study to determine whether vitamin D supplementation or high-dose supplementation (HDD) in women receiving anastrozole as adjuvant therapy for breast cancer improves aromatase inhibitor-induced musculoskeletal symptoms (AIMSS) and bone loss. Patients with early-stage breast cancer and AIMSS were stratified according to their baseline level of 25-hydroxyvitamin D [25(OH)D]. Group A (20-29 ng/mL) received HDD capsules 50,000 IU weekly for 8 weeks and then monthly for 4 months or placebo. Group B (10-19 ng/mL) received HDD for 16 weeks and then monthly for 2 months or placebo. At 2 months, all pain scale scores were improved in the HDD group compared to the placebo group. Femoral neck BMD decreased in the placebo group but was unchanged in the HDD group (p = 0.06). The study showed that weekly HDD improves AIMSS and can have a positive effect on bone density. The authors suggest that vitamin D supplementation strategies for breast cancer patients on aromatase inhibitor therapy should be investigated further [11].

Wepner et al. studied 30 women with fibromyalgia syndrome, whose serum calcifediol levels were < 32 ng/mL (80 nmol/L). The women were randomised to the treatment or control (placebo) group, with the aim of achieving serum calcifediol levels between 32 and 48 ng/mL for 20 weeks by oral supplementation with cholecalciferol. Both groups were reassessed after an additional 24 weeks without cholecalciferol supplementation. The treatment group noted a marked reduction in pain during the treatment period with a significant effect on the VAS scale scores. This was also correlated with physical role function scale scores from the *Short Form 36 Health Survey*. Optimisation of calcifediol levels in fibromyalgia syndrome had a positive effect on pain perception. The authors deemed that vitamin D therapy can be taken into consideration for patients with fibromyalgia syndrome [12].

Sakalli et al. investigated the benefits of a single dose of vitamin D, administered either orally or parenterally, on improved quality of life and functional mobility and diminished pain among elderly subjects. Community-dwelling older adult subjects over 65 years of age were included in the study. The subjects were given 300,000 IU of vitamin D, either orally or parenterally, and were assessed after 4 weeks. The subjects were divided into four groups of 30. The first group was administered IM vitamin D, the second group was administered IM placebo, the third group took vitamin D PO, and the fourth group took placebo PO. After treatment, the PTH level of the first group was reduced (p = 0.0001) and the level of vitamin D was significantly increased (P = 0.0001). In the third group, the PTH (parathormone) level was reduced (p = 0.0001), and the level of vitamin D was increased (p = 0.004) and the 24-hour calcium excretion in the urine (p = 0.015) was significantly increased. When pain,

functional mobility and quality of life were assessed, the *timed up and go* test (TUG) ($p = 0.0001$) and VAS ($p = 0.0001$) scores decreased significantly in the first group, whilst the SF-36 parameters: physical function ($p = 0.0001$), physical role (0.006), physical pain ($p = 0.0001$), general health ($p = 0.007$), social function ($p = 0.05$) and mental health ($p = 0.048$) showed significant increases. In the second group, the VAS ($p = 0.001$) decreased whilst the physical role ($p = 0.009$) and emotional role ($p = 0.034$) increased significantly. In the third group, TUG ($p = 0.0001$) and VAS ($p = 0.002$) showed a decrease, whilst physical function ($p = 0.0001$) and physical role (0.001) showed significant increases. In the fourth group, the VAS ($p = 0.007$) decreased notably. The authors concluded that administration of megadoses of vitamin D increases quality of life, decreases pain and improves functional mobility in the elderly [13].

Gendelman et al. evaluated the impact of administering 4,000 IU of vitamin D, compared to placebo, on pain and serological parameters in patients with musculoskeletal pain. Eighty patients were enrolled, and the therapy was administered for three months. Parameters were assessed at three time points: before the trial, at week 6 and at week 12. The group that received vitamin D achieved a statistically significant reduction in the VAS during the study compared to the placebo group. The need for an analgesic "rescue therapy" was significantly lower in the vitamin D-treated group. TNFα (tumour necrosis factor alpha) levels decreased by 54.3% in the vitamin D-treated group and increased by 16.1% in the placebo group. PGE2 (prostaglandin E2) decreased by 39.2% in the vitamin D-treated group and increased by 16% in the placebo group. Leukotriene B4 (LTB4) levels decreased in both groups by 24% ($p < 0.05$). According to the authors, the addition of 4,000 IU of vitamin D for patients with musculoskeletal pain may lead to a more rapid decrease in consecutive VAS scores and a decrease in the levels of inflammatory and pain-related cytokines [14].

Jin et al. compared the effects of vitamin D supplementation versus placebo on pain and knee cartilage volume in patients with symptomatic osteoarthritis and low vitamin D levels. Participants were randomly assigned to receive a monthly treatment with oral vitamin D_3 (50,000 IU: n = 209) or an identical placebo (n = 204) for 2 years. The 25-hydroxyvitamin D level increased more in the vitamin D group (40.6 nmol/L) than in the placebo group (6.7 nmol/L) ($p < 0.001$) over the 2 years. There were no significant differences in the annual change in tibial cartilage volume or in the pain scores. No significant differences were found in the change in tibiofemoral cartilage defects nor in the change in tibiofemoral bone marrow lesions. These results do not support the use of vitamin D supplementation to prevent tibial cartilage loss or to improve pain in patients with knee osteoarthritis [15].

Wu et al. conducted a study with the aim of comparing the effect of monthly high-dose vitamin D supplementation on pain impact questionnaire (PIQ-6) scores and on the prescription of analgesics in the general population. Participants, aged 50-84 years, were randomly assigned to receive monthly 100,000 IU vitamin D_3 capsules (n = 2558) or placebo (n = 2550) for a median of 3.3 years. No difference was found in the mean PIQ-6 score at the end of follow-up (adjusted mean difference: 0.06; $p = 0.82$) among participants in the vitamin D group (n = 2041) or in the placebo group (n = 2014). The proportion of participants taking one or more opioids was similar in the vitamin D group (n = 559, 21.9%) compared to placebo (n = 593, 23.3%); the relative risk (RR) adjusted for age, gender and ethnicity was 0.94 ($p = 0.24$). Similar results were observed for the administration of NSAIDs (RR = 0.94; $p = 0.24$) and other non-opioid analgesics (RR = 0.98; $p = 0.34$). Focusing on participants with vitamin D deficiency (< 50 nmol/L, 24.9%), there was a lower risk of NSAID administration in the vitamin D group compared to placebo (RR = 0.87; $p = 0.009$). All other subgroup analyses were not significant. The study showed that monthly supplementation of high-dose vitamin D neither improves the mean PIQ-6 score nor reduces analgesic intake in the general population [16].

In the recent "Palliative-D" study, Frankling et al. tested the hypothesis that correction of vitamin D deficiency may reduce opioid use in cancer patients admitted to palliative care. Patients with advanced cancer and 25-hydroxyvitamin D <50 nmol/L were randomised to 4000 IU/day of vitamin D_3 or placebo for 12 weeks. The primary endpoint was the difference in long-acting opioid use (fentanyl μg/h) between the groups over 12 weeks. The treated group of patients had a significantly lower increase in opioid doses than the placebo group ($p = 0.03$). The Fatigue reduced by vitamin D, assessed using the ESAS (Edmonton Symptom Assessment Scale), was -1.1 points after 12 weeks ($p < 0.01$). According to the authors, correction of vitamin D deficiency may have positive effects on opioid use and fatigue in patients undergoing palliative treatment for cancer, but only for those with a survival time of more than 12 weeks [17].

CONCLUSIONS

Low levels of vitamin D have been implicated in various conditions of chronic pain. Research has shown that vitamin D exerts anatomical, hormonal, neurological and immunological influences on the manifestation of pain, thus playing a role in the pathogenesis and maintenance of chronic pain states and associated comorbidity.

It is hypothesised that Vitamin D provides clinical benefits in patients with chronic pain. There are several observational studies that have shown that vitamin D supplementation provides some pain relief. Nevertheless, the results of some studies have often provided discordant outcomes. There are many reasons for these discrepancies. One point is the precise definition of serum $25(OH)D_3$ levels to determine its deficiency, normal range, and cut-off for toxicity. The difficulty in establishing pathophysiological levels of $25(OH)D_3$ deficiency has been attributed to variations in method (statistical tools), the difference in experimental assays used (technical), geographic latitude, or other variations in the individuals being studied. Hence, it has been argued that the purported "normal" range for serum $25(OH)D_3$ levels should be defined on an individual basis and within the clinical context. Serum variations may also result from genetic polymorphisms in vitamin D processing enzymes and changes in vitamin D pharmacokinetics and pharmacodynamics. Another level of complexity may arise from specific variations in the disease state of individuals, and this is particularly important in chronic pain, which shows extreme heterogeneity among individuals whilst perception of pain may be highly individualised. This latter point brings great challenges in the accurate assessment of pain especially when relying on self-reporting by the afflicted. Therefore, the development of reliable pain biomarkers that can be accurately applied to pain assessment in clinical trials is urgently needed. Hence, there is a need for large randomised con-

trolled clinical trials that can take into account the many variables involved, in order to conclusively determine the analgesic benefit of vitamin D in chronic pain and whether or not the effect is limited to patients who are vitamin D deficient.

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