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SPECIAL ARTICLE

Pleiotropic effects of vitamin D on pain: review of mechanism of action and evidence of efficacy in chronic pain

Efectos pleiotrópicos de la vitamina D en dolor: revisión del mecanismo de acción y evidencia de su eficacia en dolor crónico

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ABSTRACT:

Vitamin D is a hormone involved in multiple physiological processes both at the musculoskeletal level and in other organs and tissues. The pleiotropic (ex-bone) effects of vitamin D have shown great interest in recent years, having accumulated numerous evidence about its benefits in pathologies in which immune and/or inflammatory processes are involved. There is a broad consensus on the anti-inflammatory and immunomodulatory role of vitamin D. Considering the wide range of pleiotropic effects of vitamin D and in particular the beneficial effects it has demonstrated at the level of the central nervous system (CNS) along with its anti-inflammatory potential, its role in the treatment of pain is raised as a possibility. To this end a review of the possible mechanism of action of vitamin D in the pathophysiology of pain and the evidence of its beneficial effects on pain from clinical studies or meta-analyses has been carried out.

There is evidence of the role of vitamin D in nociception, as well as in the regulation of inflammation. The reviewed clinical evidence shows a potential benefit of vitamin D in the management of various types of pain, such as in chronic generalized pain, rheumatoid arthritis, headache, migraine, osteoarthritis pain, back pain, other types of musculoskeletal pain or diabetic neuropathy. Specifically, evidence suggests a correlation between blood vitamin D levels and the presence or intensity of pain, so monitoring and correcting these levels could result in a benefit for patients.

RESUMEN:

La vitamina D es una hormona implicada en múltiples procesos fisiológicos, tanto a nivel musculoesquelético como en otros órganos y tejidos. Los efectos pleiotrópicos (ex-óseos) de la vitamina D han despertado un gran interés en los últimos años, habiéndose acumulado numerosa evidencia sobre sus beneficios en patologías en las que los procesos inmunes y/o inflamatorios están implicados. Considerando el amplio abanico de efectos pleiotrópicos de la vitamina D y, en concreto, los efectos beneficiosos que ha demostrado a nivel del sistema nervioso central (SNC), se plantea analizar el papel que esta hormona pueda tener en el tratamiento del dolor. Para ello se ha realizado una revisión del posible mecanismo de acción de la vitamina D en la fisiopatología del dolor y se han estudiado sus efectos beneficiosos en dolor en base a la evidencia clínica disponible en estudios clínicos y metanálisis.

Existe una evidencia del papel de la vitamina D en la nocicepción, así como en la regulación de la inflamación. La evidencia clínica revisada muestra un potencial beneficio de la vitamina D en el manejo de varios tipos de dolor como, por ejemplo, en el dolor crónico generalizado, la artritis reumatoide, el dolor de cabeza, la migraña, el dolor por osteoartritis, el dolor de espalda, otros tipos de dolor musculoesquelético o la neuropatía diabética. En concreto, la evidencia sugiere una correlación entre los niveles de vitamina D en sangre y la presencia o la intensidad del dolor, por lo que la monitorización y corrección de estos niveles podría resultar en un beneficio para los pacientes.

Introduction

Vitamin D3 is a fat-soluble hormone with well-recognized functions at the musculoskeletal level that also has potential extra-skeletal effects, also called pleiotropic effects. In recent years, more than 30,000 articles have been published worldwide demonstrating a variety of beneficial effects of vitamin D, while a relatively small number have shown insufficient evidence of benefit effect at the pleiotropic level (1).

It is already recognized that almost all tissues and cells of the human body have VDR receptors (Vitamin D Receptors) and a large number of cells and tissues show activity of the enzyme 25(OH)D-1alpha hydroxylase (CYP27B1) (3) which is responsible for the bioactivation of Vitamin D by transforming it into 1,25 (OH)2D3 which is the functionally active form (2,3).

It is also known that local production of 1,25(OH)2D3 bound to VDR receptors is responsible for the regulation of approximately 2,000 genes that are involved in multiple metabolic pathways (3,4) and are responsible for several systemic benefits in different organs and tissues (2,5-13). This local production of vitamin D has been observed in different cell types including immune cells, neurons or inflammatory cells (2,3). On the other hand, there are many cells in the body that express the nuclear receptor VDR (2,3). There is also extensive evidence showing that 1,25(OH)2D3 modulates functions such as **cell growth and differentiation**, acts as an immunomodulator or regulates **the production of anti-inflammatory** cytokines (7,9,12,13) and, therefore, vitamin D deficiency, also known as VDD (*Vitamin D Deficiency*), has a great negative impact on multiple organs and systems such as the CNS, the respiratory system, the endocrine system, the immune system or the cardiovascular system among others. It has also been shown that vitamin D plays an important role in processes such as lymphatic activity, insulin production, protection against autoimmune or inflammatory diseases (7,9,12-14) and, in particular, it is indisputable that 1,25(OH)2D3 has a crucial role in endocrine, autocrine and paracrine pathways relevant in diseases such as cancer, autoimmune diseases, asthma, stroke, lupus, atopic dermatitis, Alzheimer's, infections, diabetes or metabolic syndrome, among others (5,15-19), there is even evidence to suggest that

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low vitamin D levels are significantly associated with increased mortality risk (15-19).

Considering the wide range of pleiotropic effects of vitamin D and in particular the beneficial effects it has demonstrated at the level of the CNS (central nervous system) together with its anti-inflammatory potential, its potential role in the treatment of pain is raised. To this end, a review of the possible mechanism of action of vitamin D in the pathophysiology of pain has been carried out and the evidence of its beneficial effects on pain from clinical studies or meta-analyses has been studied. A non-systematic review was conducted in PubMed of the terms vitamin D and Pain published between 2012 and 2022. Of the 219 results, the articles that were considered relevant to the objectives of this work were reviewed.

Sources of vitamin D and metabolism

There are mainly 3 sources of vitamin D:

1. Transformation of 7-dehydrocholesterol in the membrane of keratinocytes by the action of sunlight that transforms it into cholecalciferol, a natural form of Vitamin D.
2. Supplementation: of ergocalciferol (D2) or cholecalciferol (D3), the latter is the natural form that will be metabolized.
3. Food that provide vitamin D: These are scarce and amounts are usually low for normal daily intake rations.

The synthesis of vitamin D through sunlight is controversial because it is a process that is conditioned by multiple modifiable factors (surface and time of exposure without sunscreen) or non-modifiable factors (dark skin tone, north latitude of the residence location). Regarding the contribution through the diet, some studies have quantified that this is low, around 70 or 90 IU a day. It can be concluded that few patients meet the minimum exposure criteria to generate sufficient levels of vitamin D, especially in the months of November to February, in which, even when subjected to sun exposure without protector, in almost no city in Spain could generate vitamin D between the months of November to February to have a latitude close to 40° north (Cádiz 36°). Additionally, it is important to bear in mind that the absorption of vitamin D can be reduced in certain pathologies or by certain medications, such as statins.

It is important to ensure that both the healthy population and patients maintain optimal levels of circulating vitamin D. Adequate levels of vitamin D are determined by measuring the levels of 25(OH)D in the blood, which is the marker accepted as a reference and, although it is not the active form of vitamin D, it is the intermediate metabolite that is easy to measure in a routine analysis.

As for metabolism we can say that it is a process of great complexity. Although it is not the objective of this article to explain in detail all the processes of absorption, transport and metabolism of Vitamin D, we can summarize the most relevant steps (Figure 1): cholecalciferol binds to DBP proteins (*D Binding Proteins*) where it is transported to the liver to undergo a first hydroxylation by several cytochromes (mainly CYP2R1) that converts it into 25 (OH)D3 which is what we measure in blood. Subsequently, this 25(OH)D3 bound back to the DBP reaches the kidney where the DBP binds to megalin (transmembrane protein of the kidney) producing an endocytic internalization of 25(OH)D3 that is hydroxylated in the renal tubule by the action of cytochrome CYP24B1 transforming it into 1,25(OH)2D3 which is the functionally and hormonally active form that will travel to the target tissues and organs where it will exert its action through its binding to VDR receptors (14).

Vitamin D metabolism also has physiological systems that self-regulate 1,25(OH)2D3 levels to avoid potential excess toxicity. High levels of 1,25(OH)2D3 trigger a number of effects that will limit the renal metabolism, such as inhibition of PTH (parathyroid hormone, CYP27B1 stimulator) and stimulation of CYP24A1 which degrades 25(OH)D3 to 24,25(OH)2D3 and oxidizes 1,25(OH)2D3 to 1,25,26(OH)3D3 or 1,24,25(OH)3D3, all of them excretion metabolites. This self-regulation mechanism also involves levels of calcium, PTH, phosphate and other mediators such as alpha-klotho, which is a transmembrane renal protein highly expressed in the distal tubule of the kidney (14).

Mechanism of action of vitamin D in pain

Vitamin D is considered a hormone that regulates the production of anti-inflammatory cytokines, so it seems to have a relevant role in inflammatory pathologies that occur with pain. The precise mechanism by which vitamin D can exert its benefit

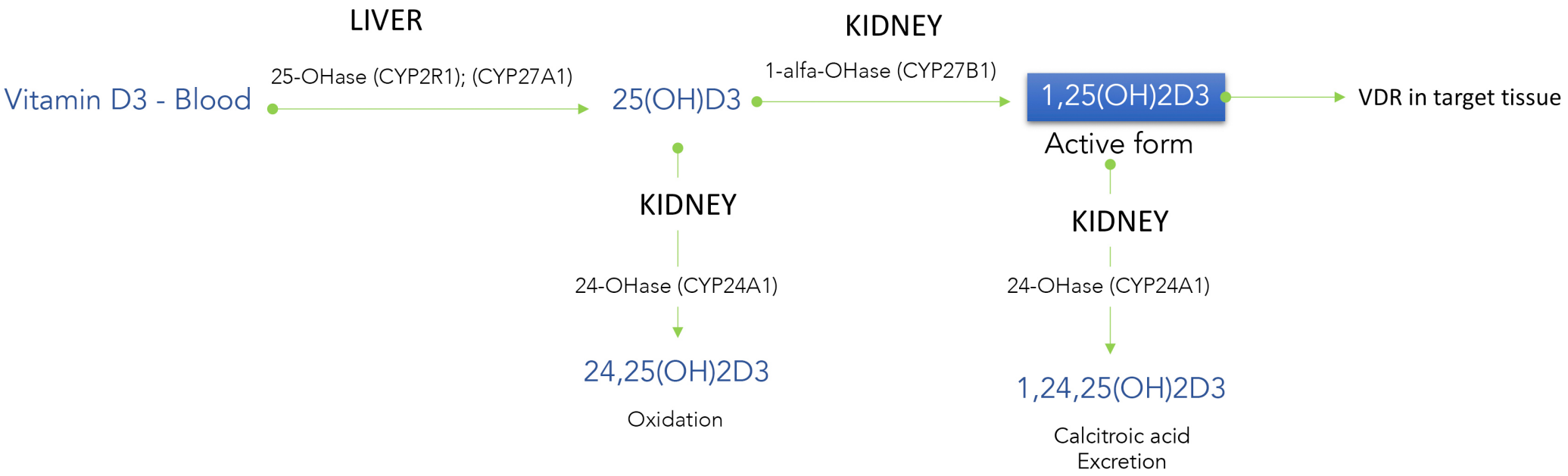

Figure 1. Simplified summary of vitamin D bioactivation and metabolism.

in pain is not well defined, but possible antinociceptive mechanisms of vitamin D have been described (21) and it would act at three levels:

1. Regulation of the inflammatory pathway: upregulation of TGF alpha, IL-4 and TNF alpha.
2. Effect on prostaglandins: inhibiting COX-2, stimulating PEGDH, inhibiting PEG2.
3. Action on neuroprotection mechanisms: upregulating the synthesis of neurotrophins and inhibiting iNOS (inducible Nitric Oxide Synthetase).

There are several studies that have been demonstrating these effects in various pathologies associated with pain and there is wide evidence showing the effects of vitamin D or its deficiency in various CNS processes.

The Gendelman study showed that vitamin D is able to reduce nociceptive input because it reduces inflammation directly related to muscle pain. It has also been shown that VDD can generate hypersensitivity in nerve fibers resulting in increased pain.

Vitamin D, being a neurosteroid, modulates different brain neurotransmitters (acetylcholine, dopamine and serotonin that are modulated by the neurotrophic activity of 1,25 (OH)2D3 (20), having a role in several brain functions, brain development, synaptic plasticity, apoptosis and amyloid clearance (21,22). Vitamin D's protective effects against neurodegeneration and cognitive decline have recently been seen (22-24).

It is also known that vitamin D affects a number of inflammatory pathways associated with the development and persistence of chronic pain, regulating the rise of transformed growth factor beta (TGF-beta 1) and interleukin 4 (IL-4) found in astrocytes and microglia (25).

The mechanism of action in fibromyalgia is one of the most studied and it is known that pain pathways associated with cortical, immunological, hormonal and neuronal changes in chronic pain are potentially influenced by vitamin D levels (20). Specifically, based on the effects of vitamin D, the following hypotheses of its mechanism of action in fibromyalgia are proposed (26) (Table I).

Table I. Summary of the 8 meta-analyses on vitamin D and chronic pain published between 2012 and 2022.

CWP: Chronic Widespread Pain. VDD: Vitamin D Deficiency.

Reference	Type of pain	Meta-analysis design	Result	Conclusions	Type of effect
Yong WC, Sanguankeo A, Upala S. Effect of vitamin D supplementation in chronic widespread pain: a systematic review and meta-analysis. Clin Rheumatol. 2017;36(12):2825-33	287 patients with CWP including fibromyalgia	4 randomized clinical studies evaluating the effect of Vitamin D	Vitamin D significantly reduced VAS vs placebo in dataset analysis	Vitamin D significantly reduced VAS vs placebo in dataset analysis	Positive
Gaikwad M, Vanlint S, Mittinity M, Moseley GL, Stocks N. Does vitamin D supplementation alleviate chronic nonspecific musculoskeletal pain? A systematic review and meta-analysis. Clin Rheumatol. 2017;36(5):1201-8	CWP	PRISMA systematic review with 3 studies	No differences were found in patients supplemented with Vitamin D	There were no differences	Neutral
Wu Z, Malihi Z, Stewart AW, Lawes CM, Scragg R. Effect of Vitamin D Supplementation on Pain: A Systematic Review and Meta-analysis. Pain Physician. 2016;19(7):415-27	Patients with chronic pain of diverse origin: myalgia, myopathy, headache, migraine, arthritis.	19 randomized studies with 3,436 participants comparing vitamin D with placebo	8 studies with 2,457 participants reported a significant reduction in pain score in the Vitamin D group (p = 0.007) The effect was greater in patients who had pre-existing pain. 4 studies non-significant trend in favor of Vitamin D	Significant reduction in pain score with vitamin D supplementation versus placebo in patients with chronic pain.	Positive
Wu Z, Malihi Z, Stewart AW, Lawes CM, Scragg R. The association between vitamin D concentration and pain: a systematic review and meta-analysis. Public Health Nutr. 2018;21(11):2022-37	Observational studies in various types of chronic pain	81 observational studies with 50,834 participants	Theconcentration of 25(OH)D was significantly lower in patients with arthritis, muscle pain or CWP (*chronic widespread pain*) but not in patients with migraine or headache	Low 25(OH)D levels may be associated with chronic pain	Positive
Zadro JR, Shirley D, Ferreira M, Carvalho Silva AP, Lamb SE, Cooper C, et al. Is Vitamin D Supplementation Effective for Low Back Pain? A Systematic Review and Meta-Analysis. Pain Physician. 2018;21(2):121-45	Patients with back pain	PRISMA meta-analysis with 8 clinical studies	There was no significant effect of vitamin D	There was no significant effect of Vitamin D	Neutral
Hoogenboom SA, Lekkerkerker SJ, Fockens P, Boermeester MA, van Hooft JE. Systematic review and meta-analysis on the prevalence of vitamin D deficiency in patients with chronic pancreatitis. Pancreatology. 2016;16(5):800-6	Patients with pancreatitis	9 studies with 465 patients with vitamin D deficiency or insufficiency in patients with pancreatitis	In patientswith pancreatitis: 83 % of patients had insufficiency and 65 % had vitamin D deficiency	High prevalence of vitamin D deficiency and insufficiency in patients with pancreatitis	Positive
Hsiao MY, Hung CY, Chang KV, Han DS, Wang TG. Is Serum Hypovitaminosis D Associated with Chronic Widespread Pain Including Fibromyalgia? A Meta-analysis of Observational Studies. Pain Physician. 2015;18(5):E877-87	CWP including Fibromyalgia	12 studies with 1,854 patients	CWP patients had significantly higher risk of VDD vs control.	Positive correlation between VDD and CWP	Positive
Wiese M, Gärtner S, Doller J, Tran QT, Frost F, Bannert K, et al. Nutritional management of chronic pancreatitis: A systematic review and meta-analysis of randomized controlled trials. J Gastroenterol Hepatol. 2021;36(3):588-600	Chronic pancreatitis	11 studies looked at various nutritional interventions, 3 of them with Vitamin D	Only vitamin D showed convincing evidence of its efficacy		Positive

It has been shown that vitamin D appears to possess anti-inflammatory properties that can alter sensitivity to peripheral pain (26-29) in fact vitamin D appears to increase muscle strength through nuclear receptors in muscle tissue. It has also been shown that VDD produces myopathy, especially in the size and number of type II muscle fibers and fat infiltration of skeletal muscles (28,30).

It has also been shown that vitamin D deficiency (< 50 mmol/L) and the degree of 25(OH)D deficiency were correlated to the degree of sensitivity to pain (29). On the other hand, a strong correlation between VDD and bone pain has also been evidenced (31).

Additionally, several studies have reported a progressive exacerbation of pain with decreased serum vitamin D levels while increasing serum vitamin D levels through adequate vitamin D supplementation, especially in patients with vitamin D deficiency, leads to improved pain relief (32).

The exact mechanisms by which vitamin D exerts this analgesic effect are not yet fully understood. A recent review by Habib et al in 2020 analyzed the possible routes in which Vitamin D acts to exert this beneficial effect such as an action at the level of the neurons of the dorsal root ganglion or the action through the VDR receptors located in the NGF (nerve growth factor) pathways, GDNF (glial-derived neurotrohpic factor), EGFR (epidermal growth factor) or even at the level of opioid receptors (32). The details of these mechanisms, as well as the function and distribution of the VDRs are not the subject of this work, but it will be of interest to review them in future articles. In any case, it seems clear that the modulating effects of vitamin D on the CNS and inflammation could explain the analgesic effect observed in some clinical studies.

Evidence in chronic pain

In the search for vitamin D and chronic pain, 19 meta-analyses and 27 clinical studies published between 2012 and 2022 were found, of which 9 meta-analyses and 11 clinical studies were considered relevant by type of population included, by the objectives or by the type of intervention studied (Tables II and III).

The potential beneficial effects of vitamin D have been demonstrated in several clinical studies, meta-analyses and reviews, although it is true that some others have shown a neutral effect (33). The 2015 Cochrane review (34) that included 10 heterogeneous studies concluded that the evidence was insufficient but that supplementation was safe and well tolerated. This lack of firm evidence can generate some controversy about the real therapeutic role of vitamin D in the treatment of pain, while we can say that there is a broad consensus regarding the excellent safety profile since supplementation has not shown toxicity effects surely due to the wide therapeutic window that vitamin D has.

In relation to the evidence that we have analyzed in chronic pain, we show below the selection of articles published in the last 10 years in which the benefit of vitamin D has been positive. One of the most recent that included chronic pain patients of diverse origins is the meta-analysis by Wu et al published in 2016 (33) which included 3,436 participants who had or developed chronic pain related to myalgia, myopathy, migraine, arthritis or headache from 19 randomized studies comparing vitamin D versus placebo. There was a significantly greater mean decrease in pain score in the vitamin D supplementation vs placebo groups (mean difference of -0.57). The effect of vitamin D was comparable in pathologies with generalized non-specific pain and localized pain. The authors concluded that a significantly greater reduction with vitamin D vs. placebo in pain scores (on pain scale) was observed in patients with chronic pain and suggest that vitamin D supplementation may have a role in chronic pain management.

Back pain

Back pain is associated with circulating inflammatory markers (35-37) especially in patients with obesity or overweight (38) and therefore therapies with anti-inflammatory properties such as vitamin D may have a relevant role in these patients (35-40). We have identified 2 meta-analyses and 6 studies that correlate vitamin D supplementation or VDD with back pain (Tables III and IV).

Recent meta-analyses have shown an association between VDD and low back pain with higher correlation in young women and in

Table II. Summary of 12 clinical studies in vitamin D and chronic pain published between 2012 and 2022.

Reference	Type of pain	Design	Result	Conclusion	Type of effect
MacFarlane LA, Cook NR, Kim E, Lee IM, Iversen MD, Gordon D, et al. The Effects of Vitamin D and Marine Omega-3 Fatty Acid Supplementation on Chronic Knee Pain in Older US Adults: Results From a Randomized Trial. Arthritis Rheumatol. 2020;72(11):1836-44	1,398 patients with chronic knee pain	Double-blind, randomized, placebo-controlled Vitamin D and Omega-3	There was no significant improvement in pain or function with any intervention	There was no improvement	Neutral
Nodler JL, DiVasta AD, Vitonis AF, Karevicius S, Malsch M, Sarda V, et al. Supplementation with vitamin D or omega-3 fatty acids in adolescent girls and young women with endometriosis (SAGE): a double-blind, randomized, placebo-controlled trial. Am J Clin Nutr. 2020;112(1):229-36	69 young people aged 12-25 with endomyetriosis and pelvic pain	Double-blind, randomized, placebo-controlled Vitamin D, Omega-3 a placebo	Patients with vitamin D had a significant improvement in pain VAS from 7 to 5.5 (p = 0.02). Placebo showed non-significant improvement	Vitamin D uplementation showed significant changes in pain	Positive
Schlögl M, Chocano-Bedoya P, Dawson-Hughes B, Orav EJ, Freystaetter G, Theiler R, et al. Effect of Monthly Vitamin D on Chronic Pain Among Community-Dwelling Seniors: A Randomized, Double-Blind Controlled Trial. J Am Med Dir Assoc. 2019;20(3):356-61	200 patients aged 70 years or older with previous fall	Double-blind, randomized to 1 year monthly treatment with: low dose (24,000 IU) high (60,000 IU) or combination of vitamin D with calcifediol (24,000 IU + 300 mcg)	58 % of participants had VDD (< 20 ng/ml) In patients with vitamin D level >20 ng/ml at the end of the study, a significant reduction in pain was observed	Baseline levels and vitamin D supplementation may be relevant in chronic pain reduction	Positive
Kenis-Coskun O, Giray E, Gunduz OH, Akyuz G. The effect of vitamin D replacement on spinal inhibitory pathways in women with chronic widespread pain. J Steroid Biochem Mol Biol. 2020;196:105488	51 patients with CWP and VDD	8 weeks of treatment with Vitamin D	Vitamin D significantly reduced the EVA y LANSS (Leeds assessment of neuropathic pain and signs pain scale) NHP (Nottingham Health Profile) improved significantly	Pain reduction and improvement of symptoms	Positive
Wu Z, Camargo CA Jr, Sluyter JD, Khaw KT, Malihi Z, Waayer D, et al. Association between serum 25-hydroxyvitamin D levels and self-reported chronic pain in older adults: A cross-sectional analysis from the ViDA study. J Steroid Biochem Mol Biol. 2019;188:17-22	5,049 patients aged 50-84 years in primary consultations with chronic pain of >6 months were analyzed	Cross-sectional analysis of the ViDA study	No differences in pain were found between patients according to 25(OH)D<50 nmol/L level	No differences according to Vitamin D level	Neutral
Akyuz G, Sanal-Toprak C, Yagci I, Giray E, Kuru-Bektasoglu P. The effect of vitamin D supplementation on pain, quality of life, and nerve conduction studies in women with chronic widespread pain. Int J Rehabil Res. 2017;40(1):76-83	33 women with CWP in VDD	Open-label study, vitamin D supplementation for 8 weeks	Significant reduction of pain scores Significant reduction in NHP pain scores, emotional reaction and physical activity	Vitamin D supplementation reduced pain and increased quality of life	Positive

(Continued on next page)

Table II. (*Cont.*) Summary of 12 clinical studies in vitamin D and chronic pain published between 2012 and 2022.

Reference	Type of pain	Design	Result	Conclusion	Type of effect
Lozano-Plata LI, Vega-Morales D, Esquivel-Valerio JA, Garza-Elizondo MA, Galarza-Delgado DA, Silva-Luna K, et al. Efficacy and safety of weekly vitamin D3 in patients with fibromyalgia: 12-week, double-blind, randomized, controlled placebo trial. Clin Rheumatol. 2021;40(8):3257-64	80 adult patients with ACR criteria for fibromyalgia.	Double-blind, randomized, placebo-controlled. Supplementation with 50,000 IU of Vitamin D per week for 12 weeks vs placebo	No statistical difference in FIQ questionnaire No difference in adverse effects	No evidence of efficacy	Neutral
Osunkwo I, Ziegler TR, Alvarez J, McCracken C, Cherry K, Osunkwo CE, et al. High dose vitamin D therapy for chronic pain in children and adolescents with sickle cell disease: results of a randomized double blind pilot study. Br J Haematol. 2012;159(2):211-5	Patients with SCD (sickle cell disease)	Pilot. Treatment with 6-week cycles with cholecalciferol 4000 to 100,000 IU per week vs placebo for 6 months	82.5 % had insufficiency and 52.5 % had vitamin D deficiency at baseline In patients with higher levels of vitamin D in blood: moredays of pain / week and higher scores of activity and quality of life in patients with higher levels of vitamin D in blood	Potential benefit of vitamin D reducing pain in patients with SCD	Positive
Alam U, Fawwad A, Shaheen F, Tahir B, Basit A, Malik RA. Improvement in Neuropathy Specific Quality of Life in Patients with Diabetes after Vitamin D Supplementation. J Diabetes Res. 2017;2017:7928083	143 patients with symptomatic diabetic neuropathy	Single IM dose of 600,000 IU of Vitamin D and follow-up every 4 weeks	41.3 % had DVD (< 20 ng/ml) Vitamin D testing significantly improved the NeuroQoL score for emotional stress but not in painful symptoms or paresthesia There was achange in the patient's perception of their quality of life	Vitamin D is effective in improving the quality of life of patients with painful diabetic neuropathy	Positive
Wepner F, Scheuer R, Schuetz-Wieser B, Machacek P, Pieler-Bruha E, Cross HS, et al. Effects of vitamin D on patients with fibromyalgia syndrome: a randomized placebo-controlled trial. Pain. 2014;155(2):261-8	30 women with fibromyalgia with VDD (<32 ng/ml)	Randomized. Treatment with oral cholecalciferol for 20 weeks to achieve levels of 32-48 ng/ml vs control	Significant significant vs. control pain significant reduction Correlation with physical functionality scores	Optimization of Vitamin D levels in blood has positive effect on pain	Positive
McCabe PS, Pye SR, Beth JM, Lee DM, Tajar A, Bartfai G, et al. Low vitamin D and the risk of developing chronic widespread pain: results from the European male ageing study. BMC Musculoskelet Disord. 2016;17:32	2339 men general population age 40 to 79 years	Study in 8 European centers with 4.3-year follow-up of Vitamin D levels and development of CWP and fibromyalgia	6.5 % developed CWP People with vitamin D levels < 15.6 ng/ml were more likely to develop CWP (OR of 1.93) than those with levels > 36.3 ng/ml	Low Vitamin D Levels Associated with Higher Risk of CWP	Positive
Yammine K, Wehbe R, Assi C. A systematic review on the efficacy of vitamin D supplementation on diabetic peripheral neuropathy. Clin Nutr. 2020;39(10):2970-4	364 patients with diabetic peripheral neuropathy	4 studies evaluating Vitamin D level and McGill pain score	Vitamin D supplementation significantly improved glycosylated hemoglobin levels and pain	Vitamin D Supplementation May Add Value to Treatment of Patients with Diabetic Peripheral Neuropathy	Positive

those with more severe vitamin D deficiency levels (25(OH)D level <12 ng/ml) (41). 19 of the 22 studies included in this meta-analysis showed that back pain was significantly more likely in patients with deficiency, severe deficiency, or low vitamin D concentrations. The association between VDD and back pain was especially clear in patients younger than 60. This association between VDD and back pain had been confirmed in previous studies such as Faraj et al (42).

Study by Zadro et al published in 2018 (43) showed 100 % resolution of low back pain in 299 patients with VDD when treated with 5,000 to 10,000 IU of Vitamin D daily for 3 months.

Table III. Summary of 3 meta-analyses on vitamin D and back pain published between 2012 and 2022.

Reference	Type of pain	Design	Result	Conclusion	Type of effect
Zadro JR, Shirley D, Ferreira M, Carvalho Silva AP, Lamb SE, Cooper C, et al. Is Vitamin D Supplementation Effective for Low Back Pain? A Systematic Review and Meta-Analysis. Pain Physician. 2018;21(2):121-45	Patients with back pain	8 clinical studies comparing different interventions	No differences	No differences	Neutral
Bansal D, Boya CS, Vatte R, Ghai B. High Prevalence of Hypovitaminosis D in Patients with Low Back Pain: Evidence from Meta-Analysis. Pain Physician. 2018;21(4):E389-E399	2,602 patients with back pain and VDD	14 studies	Higher prevalence of VDD in patients with back pain	Correction of VDD with supplementation may be added to patients with back pain	Positive
Zadro J, Shirley D, Ferreira M, Carvalho-Silva AP, Lamb SE, Cooper C, et al. Mapping the Association between Vitamin D and Low Back Pain: A Systematic Review and Meta-Analysis of Observational Studies. Pain Physician. 2017;20(7):611-40	Population with low back pain	19 estudies	Patients with back pain had significantly lower vitamin D levels This relationship was stronger in women	VDD is associated with low back pain especially in young women	Positive

Evidence suggests that patients with VDD and pain benefit from normalization of 25(OH)D levels in the blood, especially in people who are obese or overweight (44-50). It is also known that people who are obese or overweight are more likely to have VDD (51).

Regarding randomized studies in back pain, we mainly found the following: A phase III study with 9,035 women with or without VDD and post-menopause, mean age 67 years (Silva et al. 2013) (50) where it was shown that the group with VDD had significantly more back pain (69.5 % versus 66.9 %) and more cases of severe back pain (8.5 % versus 6.8 %). VDD was also significantly associated with more limitation of daily activities and more fractures. In 2019, Brady et al. (51) conducted a small study to determine the impact of vitamin D supplementation on 49 obese patients with back pain. Patients were supplemented with 4000 IU cholecalciferol daily or placebo for 16 weeks. Blood 25(OH)D levels increased significantly in the supplementation vs placebo group and patients who at baseline had low 25(OH)D levels below 30 nmol/L (12 mcg/mL) had significantly reduced back pain scores versus placebo. The authors concluded that vitamin D supplementation in patients with obesity and VDD may improve disability from back pain. The randomized, double-blind, placebo-controlled study by Gendelman et al (52) studied the effect of cholecalciferol 4,000 IU daily versus placebo in 80 patients with musculoskeletal pain for 3 months. Vitamin D significantly reduced VAS versus placebo. The need for rescue medication was significantly lower in the Vitamin D group. A 54.3 % reduction in TNF-alpha levels versus a 16 % increase in the placebo group was also observed, as well as a 39.2 % reduction in PEG2 versus a 16 % increase with placebo. The authors concluded that vitamin D can reduce the level of pain quickly and reduce levels of inflammatory cytokines.

Pain in patients with osteoarthritis (OA)

In the case of osteoarthritis there is abundant evidence of the benefit of vitamin D at the musculoskeletal level as well as the importance of maintaining sufficient levels of 25(OH)D in the blood. The effects of vitamin D in OA are not limited to its musculoskeletal benefits but there is evidence of its effect

Table IV. Summary of 7 clinical studies in vitamin D and back pain published between 2012 and 2022.

Reference	Type of pain	Design	Result	Conclusion	Type of effect
Brady SRE, Naderpoor N, de Courten MPJ, Scragg R, Cicuttini F, Mousa A, et al. Vitamin D supplementation may improve back pain disability in vitamin D deficient and overweight or obese adults. J Steroid Biochem Mol Biol. 2019;185:212-7	49 overweight or obese adults in VDD (<50 nmol/L) tested with back pain	Randomized. 100,000 IU of Vitamin D placebo for 15 weeks	In the group with 25(OH)D levels < 30 nmol/L there was significant reduction in pain and disability with vitamin D vs. placebo	Vitamin D supplementation in overweight-obese patients and VDD may improve pain and functionality from back pain	Positive
Ghai B, Bansal D, Kanukula R, Gudala K, Sachdeva N, Dhatt SS, et al. Vitamin D Supplementation in Patients with Chronic Low Back Pain: An Open Label, Single Arm Clinical Trial. Pain Physician. 2017;20(1):E99-E105	68 patients with chronic back pain and VDD (<30 ng/ml)	Open. Supplementation with 60,000 IU every 8 weeks for 6 months	66 % of patients reached normal levels (< 29 ng/ml) Significant reduction in pain VAS and function at months 2, 3, and 6 vs. basal	Vitamin D supplementation may improve pain and function in patients with chronic back pain and VDD	Positive
Ghai B, Bansal D, Kapil G, Kanukula R, Lavudiya S, Sachdeva N. High Prevalence of Hypovitaminosis D in Indian Chronic Low Back Patients. Pain Physician. 2015;18(5):E853-62	328 patients with chronic back pain	Relationship between VDD and pain	86 % of patients had VDD There wasa significant relationship between VDD and functional disability	Prevalence of VDD correlates with dysfunction in back pain	Positive
Sandoughi M, Zakeri Z, Mirhosainee Z, Mohammadi M, Shahbakhsh S. The effect of vitamin D on nonspecific low back pain. Int J Rheum Dis. 2015;18(8):854-8	53 patients with non-specific back pain	Double-blind, randomized. Treatment with 50,000 IU of Vitamin D per week for 8 weeks vs placebo	Asignificant reduction of pain, with VAS reduction from 5.42 to 3.03 in the Vitamin D group. Similar reduction in placebo group.	Vitamin D and placebo improved pain	Neutral
e Silva AV, Lacativa PG, Russo LA, de Gregório LH, Pinheiro RA, Marinheiro LP. Association of back pain with hypovitaminosis D in postmenopausal women with low bone mass. BMC Musculoskelet Disord. 2013;14:184	9,305 patients with back pain and menopause evaluated	Ratio of VDD and back pain	22.5 % of participants had VDD Patients with VDD had significantly more back pain, more fractures and greater difficulty in daily activities	VDD correlates with back pain, its severity and disruption of daily activity	Positive
Gendelman O, Itzhaki D, Makarov S, Bennun M, Amital H. A randomized double-blind placebo-controlled study adding high dose vitamin D to analgesic regimens in patients with musculoskeletal pain. Lupus. 2015;24(4-5):483-9	80 patients with musculoskeletal pain	Double-blind, randomized, placebo-controlled. 4,000 IU cholecalciferol daily vs placebo for 3 months.	Significant reduction in VAS vs. placebo pain Significantly reduced need for rescue analgesia Reduction of TNF alpha levels by 54.3 % vs. increase of 16 % in placebo PGE2 reduction by 39.2 % vs. 16 % increase in placebo	Supplementation with 4,000 IU per day of Cholecalciferol may result in a greater decrease in pain (VAS) and reduction of pro-inflammatory and pain-related cytokines	Positive
Al Faraj S, Al Mutairi K. Vitamin D deficiency and chronic low back pain in Saudi Arabia. Spine (Phila Pa 1976). 2003;28(2):177-9	260 patients Chronic idiopathic low back pain	6-year follow-up to study relationship of VDD, pain and supplementation with Vitamin D	83 % of patients had low levels of vitamin D before supplementation Supplementation treatment improved levels	VDD is a major contributor to chronic pain	Positive

in reducing pain, improving functionality or reducing disease progression. We have identified 6 meta-analyses and 3 randomized studies published between 2012-2022 in which the impact of vitamin D on pain and function of these patients is evaluated (Tables V and VI). We show below the most relevant meta-analyses that studied the effect on pain: a meta-analysis of 28 randomized studies with 11,890 patients with knee OA in which the effect of various treatments was studied (53).

Table V. Summary of 6 meta-analyses on vitamin d and osteoarthritis (OA) pain published between 2012 and 2022.

WOMAC: Western Ontario McMaster Universities Osteoarthritis Index

Reference	Type of pain	Design	Result	Conclusion	Type of effect
Yu Y, Liu D, Feng D, Zhao J. Association between Vitamin D and Knee Osteoarthritis: A PRISMA-Compliant Meta-analysis. Z Orthop Unfall. 2021;159(3):281-7	OA knee	PRISMA meta-analysis	No significant association between serum vitamin D levels and OA incidence Significant association of low vitamin D levels with OA progression	Evidence of possible association with OA progression No difference between VDD and OA risk	Neutral-Positive
Zhao ZX, He Y, Peng LH, Luo X, Liu M, He CS, et al. Does vitamin D improve symptomatic and structural outcomes in knee osteoarthritis? A systematic review and meta-analysis. Aging Clin Exp Res. 2021;33(9):2393-403	1,599 patients with knee OA	6 items with Vitamin D supplementation	Redución significativa del WOMAC score incluyendo el WOMAC-pain, WOMAC-function score y WOMAC-stiffenss score Supplementation with 2000 IU was significantly associated with reduced progression	Vitamin D Supplementation May Improve WOMAC Pain and Functionality	Positive
Yang W, Sun C, He SQ, Chen JY, Wang Y, Zhuo Q. The Efficacy and Safety of Disease-Modifying Osteoarthritis Drugs for Knee and Hip Osteoarthritis-a Systematic Review and Network Meta-Analysis. J Gen Intern Med. 2021;36(7):2085-93	11,890 patients with OA	28 randomized studies with several interventions, including Vitamin D	Vitamin D showed significant improvement in pain and function	Vitamin D improves symptoms	Positive
Diao N, Yang B, Yu F. Effect of vitamin D supplementation on knee osteoarthritis: A systematic review and meta-analysis of randomized clinical trials. Clin Biochem. 2017;50(18):1312-6	1130 patients with OA knee	4 clinical studies comparing vitamin D supplementation and placebo	Vitamin D supplementation had small-medium but significant effect on pain	Significantly improves pain	Positive
Beaudart C, Lengelé L, Leclercq V, Geerinck A, Sanchez-Rodriguez D, Bruyère O, et al. Symptomatic Efficacy of Pharmacological Treatments for Knee Osteoarthritis: A Systematic Review and a Network Meta-Analysis with a 6-Month Time Horizon. Drugs. 2020;80(18):1947-59	15,609 patients with OA	80 randomized studios. 6 months	Significant reduction of pain and significant functional improvement with Vitamin D	6 months of Vitamin D treatment can improve pain and function	Positive
Gao XR, Chen YS, Deng W. The effect of vitamin D supplementation on knee osteoarthritis: A meta-analysis of randomized controlled trials. Int J Surg. 2017;46:14-20	1,136 patients	4 randomized studios.	Vitamin D supplementation doses of at least 2,000 IU/day were associated with significant reduction in WOMAC-pain and WOMAC-functionality, but not in stiffness	Vitamin D Supplement May Improve Pain and Function	Positive

Vitamin D improved patients' pain and function. Another meta-analysis of 79 studies involving 15,609 patients in which various treatments were tested. 4 studies with 498 patients studied the effect of vitamin D on pain and 4 studies with 571 patients studied the effect of vitamin D on functionality (54). Vitamin D is effective in reducing pain and shows a significant improvement in functionality in 6-month treatments.

Finally, another meta-analysis of 6 studies with 1,599 patients with knee OA (55) showed that vitamin D supplementation significantly improves WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) including the outcome of pain (-0.32), functionality (-0.34) and stiffness (-0.13). The authors concluded that vitamin D supplementation can improve function and pain.

Table VI. Summary of 4 randomized-controlled studies in vitamin d and osteoarthritis (OA) pain published between 2012 and 2022.

Reference	Type of pain	Design	Result	Conclusion	Type of effect
MacFarlane LA, Cook NR, Kim E, Lee IM, Iversen MD, Gordon D, et al. The Effects of Vitamin D and Marine Omega-3 Fatty Acid Supplementation on Chronic Knee Pain in Older US Adults: Results From a Randomized Trial. Arthritis Rheumatol. 2020;72(11):1836-44	1,398 patients with OA knee	Double-blind, placebo-controlled. Vitamin D and Omega3 (VITAL)	There was no significant reduction in pain or functional improvement	No effect on pain	Neutral
Tu L, Zheng S, Cicuttini F, Jin X, Han W, Zhu Z, et al. Effects of Vitamin D Supplementation on Disabling Foot Pain in Patients With Symptomatic Knee Osteoarthritis. Arthritis Care Res (Hoboken). 2021;73(6):781-7	340 patients with symptomatic knee OA completed study	Double-blind, randomized, Vitamin D vs Placebo for 2 years	23.7% had disabling standing pain. La Vitamina D mejoró significativamenten los scores de MFPDI (Manchester Foot Pain and Disability) a 2 años vs placebo The improvement was greater in patients who maintained sufficient levels vs low levels of Vitamin D	Vitamin D supplementation and maintenance of sufficient vitamin D levels may improve foot pain	Positive
McAlindon T, LaValley M, Schneider E, Nuite M, Lee JY, Price LL, et al. Effect of vitamin D supplementation on progression of knee pain and cartilage volume loss in patients with symptomatic osteoarthritis: a randomized controlled trial. JAMA. 2013;309(2):155-62	146 patients with OA knee	Double-blind, randomized, placebo-controlled at 2 years. Vitamin D supplementation	The baseline pain level was worse in the VitaminD group and functionality was significantly worse in the Vitamin D group. Pain was reduced in both groups with no difference between them.	2-year vitamin D supplementation at doses sufficient to reach 36 ng/ml reduced pain to the same extent as placebo	Neutral
Sanghi D, Mishra A, Sharma AC, Singh A, Natu SM, Agarwal S, et al. Does vitamin D improve osteoarthritis of the knee: a randomized controlled pilot trial. Clin Orthop Relat Res. 2013;471(11):3556-62	107 patients with OA knee and VDD (<50 nmol/l)	Pilot studio, randomized, controlled. Vitamin D supplement placebo at 12 months	Reduction of knee pain with Vitamin D in both VAS and WOMAC vs increased pain with placebo Improved knee vs placebo functionality	Small but significant clinical benefit with Vitamin D	Positive

Chronic widespread pain (CWP)

CWP is a very heterogeneous and difficult to manage pathology. There is evidence of the potential benefit of vitamin D in these patients (Tables II and III) and we show below the most relevant: A recent European cohort of 2,313 men followed for 4.3 years (56). An increased risk of developing CWP was observed in patients with lower blood vitamin D levels (< 15.6 ng/ml) vs. the group with levels above 36.3 ng/ml. A meta-analysis of 12 studies involving 1,854 patients with CWP vs control (57) showed significantly increased risk of DVD in patients with CWP. Another meta-analysis of 4 randomized studies including 287 patients with CWP (including fibromyalgia) (58) showed that patients on vitamin D had significantly lower pain score (VAS) than patients on placebo. A meta-analysis of 81 observational studies involving 50,834 patients comparing vitamin D concentration in various pathologies (59) showed that the concentration of 25(OH) D was significantly lower in patients with arthritis, muscle pain or CWP.

Other types of pain

There is also evidence in other types of pain, especially related to rheumatological pathologies. The most relevant studies are presented below: a meta-analysis of 8 randomized

studies in patients with rheumatoid pathology (rheumatoid arthritis, spondylarthritis, psoriatic arthritis) in which Vitamin D analysis was included (60). Vitamin D may reduce complications in such patients and the authors conclude that vitamin D should be given in patients with deficiencies to prevent musculoskeletal complications. Another meta-analysis of 7 studies involving 2,420 statin-treated patients comparing the group with and without myalgia (61). Vitamin D concentrations were significantly lower in patients with myalgia. The prospective, multicenter, observational DESIR study in 700 patients with vitamin D deficiency (< 25 ng/ml) for 2 years (62). It showed that VDD was significantly associated with the presence of sacroiliitis, higher ASDAS[1] (Ankylosing Spondylitis Disease Activity Score), higher BASDAI (Bath Ankylosing Spondylitis Disease Activity Index)[1] obesity and metabolic syndrome. The meta-analysis by Yammine et al. (63) showed benefit of vitamin D supplementation in patients with diabetic peripheral neuropathy both in reducing pain (-48.5 % of VAS and reduction of the score according to the McGill pain questionnaire) as well as the significant improvement of the NSS (neuropathy symptom score) concluding the authors that vitamin D can be added to the usual treatment of diabetic peripheral neuropathy to improve pain treatment. The systematic review of vitamin D supplementation in pain, disease activity, functional status and relapse ratio in RA patients (Bella et al.) showed that correction of VDD may be beneficial in pain. Achieving adequate plasma levels of vitamin D may show immunomodulatory effects with a positive impact on pathology (64).

Headache and migraine

There are several studies and reviews on the potential benefit of Vitamin D in migraine or headache (Tables VII and VIII). Most show positive effect, although some of them were neutral. The most relevant ones that have shown beneficial effect are presented here: Some observational studies have established an inverse relationship between vitamin D levels and headaches (both migraine and TTH) (65-72). Another study found no relationship between migraine and vitamin D but found an inverse correlation between the risk of non-migraine headache and vitamin D levels (73). A recent 2020 double-blind, randomized, placebo-controlled study showed that supplementation with 2,000 IU per day of vitamin D for 12 weeks in patients with episodic migraine reduced disability outcomes even after controlling for baseline vitamin D levels. The mean number of migraine days was also significantly reduced, with this reduction being greater in patients who had migraine with aura (73). In the year 2020 Fallah et al. study in 57 children and adolescents with migraine were randomized with topiramate 2 mg/kg daily combined with Vitamin D3 500,000 IU weekly for 2 months versus topiramate monotherapy. Efficacy in reducing headache frequency, intensity, duration, and disability was observed in both groups, but the combination of topiramate plus vitamin D was more effective than topiramate alone (74). The reviewof Ghorbani et al in 2019 (75) showed that between 45 % and 100 % of patients with headache or migraine have VDD or vitamin D insufficiency. The studies also showed an inverse relationship between vitamin D levels and the frequency of pain. Finally, this review showed that supplementation with doses of 1,000 to 4,000 IU per day could reduce the frequency of migraine attacks.

Conclusions

The benefits of maintaining sufficient levels of vitamin D in the blood have been widely described in many clinical situations and it is widely demonstrated that this hormone is necessary for the proper functioning of many physiological processes.

In the case of pain, there is evidence of its role in nociception, as well as its role as a regulator of inflammation. Clinical evidence shows a potential benefit of vitamin D in the control of pain of various kinds, as shown in this work, although it is true that there are some studies that show a neutral effect on pain, other studies have shown a clear benefit in the control of pain and inflammation. These beneficial effects have been seen in numerous studies and in various types of pain such as chronic generalized pain, back pain, rheumatoid arthritis pain, headache, migraine, osteoarthritis pain, other types of musculoskeletal pain or diabetic peripheral neuropathy among others.

Evidence also suggests that there is a correlation between blood VD levels and the presence or intensity of pain, so normalizing these levels could result in a benefit in patients with pain.

[1] These are two of the scales used to measure disease activity in patients with ankylosing spondylitis. More information about this scale at: https://basdai.com

Table VII. Summary of 3 meta-analyses of vitamin D and pain in patients with confirmed migraine published between 2012 and 2022.

Reference	Type of pain	Design	Result	Conclusion	Type of effect
Liampas I, Siokas V, Brotis A, Dardiotis E. Vitamin D serum levels in patients with migraine: A meta-analysis. Rev Neurol (Paris). 2020;176(7-8):560-70	Migraine patients vs healthy control	8 studies with 25(OH)D level determination	Vitamin D levels were significantly lower in migraine vs healthy patients	Association between migraine and VDD	Positive
Hu C, Fan Y, Wu S, Zou Y, Qu X. Vitamin D supplementation for the treatment of migraine: A meta-analysis of randomized controlled studies. Am J Emerg Med. 2021;50:784-8	301 migraine patients	6 studies studied vitamin D supplementation	Significant reduction in pain and attacks per month, number of days with pain per month and MIDAS score No influence on attack duration or severity	Vitamin D Supplementation May Be Beneficial in Migraine Treatment	Positive
Zhang YF, Xu ZQ, Zhou HJ, Liu YZ, Jiang XJ. The Efficacy of Vitamin D Supplementation for Migraine: A Meta-Analysis of Randomized Controlled Studies. Clin Neuropharmacol. 2021;44(1):5-8	Migraine patients	5 randomized studies comparing Vitamin D vs control treatment	Vitamin D is associated with significant reduction of pain days, frequency of attacks, severity and MIDAS score	Vitamin D is effective in relieving migraine	Positive

Marchesi et al. himself in 2022 (21) concluded that given the prevalence of VDD in patients with chronic pain, vitamin D supplementation offers numerous health benefits. The existing evidence is insufficient to consider that vitamin D can currently be an effective treatment in chronic pain independently. Helde-Frankling et al. recommended as early as 2017 (76) that patients with 25(OH) D levels below 12 ng/ml can benefit most from supplementation while those with levels above 50 ng/ml may have a lower benefit. "Our conclusion is that vitamin D is a simple, safe and potentially beneficial way to reduce pain in patients with VDD, although more randomized, placebo-controlled studies are needed before firm conclusions can be drawn".

There are no formal recommendations from scientific societies regarding the use of Vitamin D supplements to improve pain control, although a task force of EULAR (European Alliance of Associations for Rheumatology) has published in 2022 a review of the effects of nutritional and lifestyle products for patients with musculoskeletal and rheumatic diseases where it recognizes a moderate beneficial effect of vitamin D on pain and activity of the disease (77).

This brief review work seems to confirm this conclusion and we can say, therefore, that in patients with VDD it could be beneficial to normalize their levels of vitamin D in blood through supplementation, these benefits being the reduction of pain and the possible functional improvement.

Considering this potential benefit of vitamin D and its excellent margin of safety, it can be suggested that supplementation with vitamin D, specifically with the natural form (cholecalciferol), could be added to the standard therapeutic treatment of pain that the patient is following. The mechanisms of action of vitamin D, as well as the distribution of VDR receptors could explain the benefits seen in clinical studies, but it is necessary to deepen the knowledge of these mechanisms, as well as the collection of more scientific evidence.

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Table VIII. Summary of 5 randomized studies in vitamin D and pain in patients with confirmed migraine published between 2012 and 2022.

Reference	Type of pain	Design	Result	Conclusion	Type of effect
Ghorbani Z, Togha M, Rafiee P, Ahmadi ZS, Rasekh Magham R, Djalali M, et al. Vitamin D3 might improve headache characteristics and protect against inflammation in migraine: a randomized clinical trial. Neurol Sci. 2020;41(5):1183-92	80 patients with episodic migraine	Doble-Blind. Vitamin D supplement 2,000 IU daily or placebo for 12 weeks	Vitamin D significantly reduced the number of headache days/month (4.71), reduced the duration of attacks (12.99 h), pain severity (VAS 5.47) and reduced analgesic use per month (2.85) vs placebo (6.43, 18.32, 6.38 and 4.87 respectively)	Vitamin D 2,000 IU daily for 12 weeks may improve migraine and may reduce neuroinflammation	Positive
Ghorbani Z, Rafiee P, Fotouhi A, Haghighi S, Rasekh Magham R, Ahmadi ZS, et al. The effects of vitamin D supplementation on interictal serum levels of calcitonin gene-related peptide (CGRP) in episodic migraine patients: post hoc analysis of a randomized double-blind placebo-controlled trial. J Headache Pain. 2020;21(1):22	80 patients with episodic migraine with aura	Double-blind, randomized, placebo-controlled. 12 weeks of Vitamin D 2,000 IU per day or placebo	Vitamin D significantly improved MIDAS vs placebo score. CGRP levels were significantly lower with vitamin D (calcitoning gene-related peptide which is the dominant mediator in migraine pain pathogenesis)	Supplementation with Vitamin D improves headache and disability in migraine	Positive
Gazerani P, Fuglsang R, Pedersen JG, Sørensen J, Kjeldsen JL, Yassin H, et al. A randomized, double-blinded, placebo-controlled, parallel trial of vitamin D3 supplementation in adult patients with migraine. Curr Med Res Opin. 2019;35(4):715-23	36 women with migraine	Double-blind, randomized, placebo-controlled Vitamin D placebo for 24 weeks	Vitamin D significantly reduced migraine frequency vs placebo.	Vitamin D was superior to placebo by reducing migraine days	Positive
Cayir A, Turan MI, Tan H. Effect of vitamin D therapy in addition to amitriptyline on migraine attacks in pediatric patients. Braz J Med Biol Res. 2014;47(4):349-54	53 patients aged 8-16 years with migraine	Vitamin D +/- Amitriptyline Group 1: No Vitamin D in patients with normal level, G2:400 IU/day in patients with normal levels, G3: 800 IU/day in patients with deficiency and G4: 5,000 IU per day in patients with severe deficiency 6 months	Vitamin D reduces the number of migraine attacks vs baseline data	Vitamin D May Reduce the Number of Migraine Attacks	Positive
Fallah R, Sarraf Yazd S, Sohrevardi SM. Efficacy of Topiramate Alone and Topiramate Plus Vitamin D3 in the Prophylaxis of Pediatric Migraine: A Randomized Clinical Trial. Iran J Child Neurol. 2020;14(4):77-86	57 Patients 5 to 15 years with migraines	Randomized comparing Topiramate 2 mg/kg al día +/- Vitamin D 500,000 IU/week for 2 months	Both treatments were effective in reducing the frequency, severity, duration and disability of migraines. The combination of Topiramate + Vitamin D was significantly more effective than Topiramate alone: attack frequency 6.12 vs 9.87; Disability score 19.24 versus 22.11. Good response to treatment in 60.7% of topiramate alone vs 75.9% of topiramate + Vitamin D.	The combination of topiramate + Vitamin D is safe and effective in migraine prophylaxis in children	Positive

expression of white blood cells: a randomized double-blind clinical trial. PLoS One. 2013;8(3):e58725. DOI: 10.1371/journal.pone.0058725.

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