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The Relationship between Vitamin D Deficiency and Chronic Pain: Systematic Review

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ABSTRACT

Objectives: To gather and assess current studies on how a lack of vitamin D relates to chronic pain. Methods: A total of 632 pertinent publications were found after a comprehensive search across four databases. 34 full-text publications were examined after duplicates were eliminated using Rayyan QCRI and relevance was checked; eight studies finally satisfied the requirements for inclusion. Results: We included eight studies with a total of 357,366 participants, and 166,565 (46.6%) were males. The prevalence of vitamin D deficiency ranged from 1.5% to 82.3% in patients with chronic pain. Many people with chronic pain have low levels of vitamin D, but it's not clear if this deficiency causes the pain. In some groups, lower vitamin D levels were linked to more severe pain, possibly because of inflammation shown by higher inflammatory markers in certain cases. However, results have been mixed, with some studies finding no direct connection between vitamin D levels and ongoing chronic pain. These findings emphasize the importance of more research to understand how vitamin D affects chronic pain and whether supplements could be a potential treatment. Conclusion: This review highlights a potential link between vitamin D deficiency and chronic pain, especially in cases of widespread musculoskeletal pain. While it's not definitively proven that vitamin D deficiency causes this pain, it seems to make it worse for some groups of people, possibly by triggering inflammation. Checking vitamin D levels in patients with chronic pain could be a helpful part of their treatment plan. Future studies should aim to conduct thorough and long-term research to better understand how vitamin D deficiency and chronic pain are connected and evaluate the effectiveness of supplementation as a treatment option.

KEYWORDS: Vitamin D; Deficiency; Chronic pain; Systematic review.

1. Introduction

"An unpleasant feeling or sensation associated with actual or potential damage to

tissues, or described in terms of such damage," is how the International Association for the Study of Pain defines pain [1]. The most frequent cause of primary care visits and medical consultations is pain, or disorders where pain is a major symptom, such as chronic, broad pain, musculoskeletal pain (such as lower back pain), arthritis, and headaches [2, 3]. Depending on the community under study, the prevalence of chronic pain might range from 8% to 60% and higher [4].

According to recent evaluations of painful illnesses, the prevalence of fibromyalgia in the general population ranges from 2 to 8% [5], whereas the prevalence of lower back pain is 9·4% [6], rheumatoid arthritis is 0·24% [7], and present migraine is more than 10% in adults worldwide [3]. For patients and the health system, painful conditions can have a significant negative impact on quality of life, cause work incapacity, and result in significant financial burdens [2, 3, 4, 6, 8].

The precursors of 1,25-dihydroxyvitamin D3, commonly referred to as calcitriol, the active secosteroid hormone, are referred to as vitamin D [9]. Despite being categorized as a fat-soluble vitamin, calcitriol is not a vitamin because the body can produce it [10]. Sunlight exposure, particularly ultraviolet B radiation, and vitamin D supplementation are the only two ways to obtain vitamin D in the amounts required for good health [9, 10]. Food and food are not regarded as adequate sources of vitamin D because they do not contain enough of it to be helpful [9].

Chronic pain is a tough and widespread health problem that has a big impact on people's lives mental health, and ability to function. It often needs a lot of care and uses up a lot of healthcare resources. Even though researchers keep looking for ways to ease pain many people still cannot find long-term relief that works. New studies have found a possible link between not having enough vitamin D and chronic pain. They think that low levels of this important nutrient might affect how people feel pain how inflammation happens, and how healthy their muscles and bones are. We know vitamin D is key for strong bones and a good immune system. It also helps fight inflammation and protect nerves, which might change how sensitive people are to pain. But we are not sure how this works. Different studies have found different things, and sometimes they do not agree. Because this could be so important for stopping and treating chronic pain, we need to take a close look at all the research. We want to see if not having enough vitamin D does make chronic pain more likely to start or keep going. If we can figure this out, it could lead to new ways to treat pain for people who are more likely to have low vitamin D and chronic pain. This systematic review aims to gather and assess current studies on how a lack of vitamin D relates to chronic pain.

2. Methods

Search strategy

The PRISMA and GATHER criteria were adhered to in the systematic review. To locate pertinent research on the association between vitamin D deficiency and chronic pain, a comprehensive search was carried out. Four electronic databases were searched by the reviewers: SCOPUS, Web of Science, Cochrane, and PubMed.

Included studies were within the last 5 years between 2019-2024. We eliminated any duplicates and uploaded all of the abstracts and titles that we could find using electronic searches into Rayyan. After that, all of the study texts that met the requirements for inclusion based on the abstract or title were gathered for a thorough examination. Two reviewers independently assessed the extracted papers' suitability and discussed any discrepancies.

Study population—selection

The PEO (Population, Exposure, and Outcome) factors were implemented as inclusion criteria for our review: (i) Population: General population or patients with chronic conditions, (ii) Intervention: Vitamin D deficiency, (iii) Outcome: Chronic pain.

Data extraction

Data from studies that satisfied the inclusion requirements were extracted by two objective reviewers using a predetermined and uniform methodology. The following information was retrieved and recorded: (i) First author (ii) Year of publication, (iii) Study design, (iv) Participants' number, (v) Age, (vi) Gender, (vii) Pain type, (viii) Follow-up period (in months), (ix) Mean vitamin D level, (x) Prevalence of vitamin D deficiency, (xi) Main outcomes.

Quality review

Since bias resulting from omitted factors is frequent in studies in this field, we used the ROBINS-I technique to assess the likelihood of bias since it enables a thorough examination of confounding. The ROBINS-I tool can be used for cohort designs where individuals exposed to different staffing levels are tracked over time and is designed to assess non-randomized studies. Each paper's risk of bias was evaluated independently by two reviewers, and any differences were settled by group discussion [11].

3. Results

The specified search strategy yielded 632 publications (Figure 1). After removing duplicates (n =311), 321 trials were evaluated based on title and abstract. Of these, 287 failed to satisfy eligibility criteria, leaving just 34 full-text articles for comprehensive review. A total of 8 satisfied the requirements for eligibility with evidence synthesis for analysis.

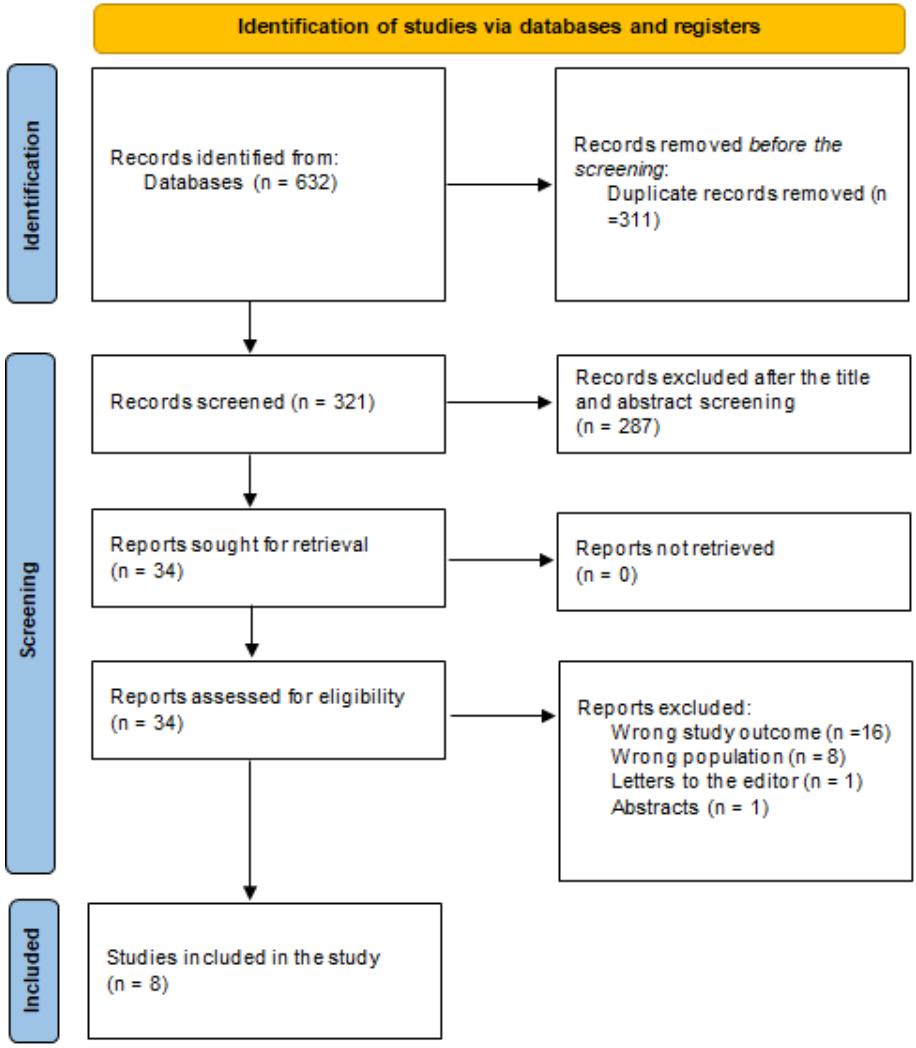

Figure (1): PRISMA flowchart [12].

Sociodemographic and clinical outcomes

We included eight studies with a total of 357,366 participants, and 166,565 (46.6%) were males. Regarding study designs, seven studies were cross-sectionals, and only one was a case-control [18]. Two studies were implemented in China [15, 19], two in Pakistan [16, 18], one in The UK [14], one in The USA [17], one New Zealand [20], and one in India [21].

The prevalence of vitamin D deficiency ranged from 1.5% [20] to 82.3% [16] in patients with chronic pain. Research showed a connection between not having enough vitamin D and a higher chance of feeling pain all over, not just in one spot [15, 17, 19, 21]. But some studies did not find any link between vitamin D levels and

ongoing pain, which means vitamin D might not affect how people feel specific types of long-lasting pain, like lower back pain that will not go away [14, 16, 18, 20].

A lot of people with chronic pain had low vitamin D in many studies, which points to a possible link but does not prove that one causes the other. For example, some research found that bone loss and osteoporosis were not related to how much vitamin D someone had [15].

In some cases, not having enough vitamin D went hand in hand with worse pain for certain groups, like some ethnic groups where people with less vitamin D reported more pain [17]. Also, people with low vitamin D and ongoing lower back pain without a clear cause had more signs of inflammation in their bodies. This could mean inflammation might be how vitamin D levels and pain are connected. But since not all studies found a clear cause-and-effect relationship, it seems that while not having enough vitamin D might make pain worse in some situations, this is not true for all types of long-lasting pain.

Table (1): Outcome measures of the included studies

Study ID	Study design	Country	Sociodemographic	Pain type	Follow-up (months)	Mean vitamin D	Vitamin D deficiency	Main outcomes
Xie et al., 2024 [14]	Cross-sectional	UK	N: 349,221 Mean age: 56.9 Males: 162,388 (46.5%)	Chronic musculoskeletal pain	3	NM		Although it was not linked to chronic regional musculoskeletal pain at the neck/shoulder, back, hip, or knee, severe vitamin D insufficiency was nonetheless substantially linked to an elevated risk of chronic broad pain.
Duan et al., 2020 [15]	Cross-sectional	China	N: 184 Mean age: 57.6 Males: 49 (26.6%)	Chronic pain	NM	13.8 ± 7.2	106 (57.7%)	Patients with chronic pain frequently have vitamin D deficiency, and severe vitamin D deficiency is not unusual. Osteoporosis and bone mass loss are not associated with vitamin D levels.
Kumar et al., 2020 [16]	Cross-sectional	Pakistan	N: 1152 Mean age: 41.7 Males: 520 (45.1%)	Chronic low back pain	3	22.7 ± 13.8	948 (82.3%)	Vitamin D levels did not correlate with persistent low back discomfort.
Overstreet et al., 2022 [17]	Cross-sectional	USA	N: 156 Mean age: 45.5 Males: 63 (40.4%)	Chronic low back pain	3	22.9 ± 11.2	70 (44.9%)	In a sample of people with persistent low back pain, vitamin D insufficiency

								may be associated with increased pain severity, particularly for those who determine as Non-Hispanic Black.
Ghani et al., 2023 [18]	Case-control	Pakistan	N: 159 Mean age: 44.6 Males: 63 (39.9%)	Chronic low back pain	NM	23.2 ± 17.8	118 (74.2%)	Hypovitaminosis D and chronic low back pain are not causally related.
Hao-Wei et al., 2021 [19]	Cross-sectional	China	N: 198 Mean age: 63.4 Males: 72 (36.3%)	Chronic low back pain	6	18.3 ± 8.1	97 (48.9%)	Vitamin D levels were lower and inflammatory marker levels were higher among individuals with nonspecific chronic low back pain. IL-6 may act as a mediator in the relationship between hypovitaminosis D and non-specific persistent low back pain.
Wu et al., 2019 [20]	Cross-sectional	New Zealand	N: 5920 Mean age: 66 Males: 3367 (56.9%)	Chronic pain	12	NM	90 (1.5%)	Both before and after adjusting for confounders, there was no correlation between the prevalence of chronic pain in older persons and baseline 25(OH)D levels.
Kumar Yadav et al., 2021 [21]	Cross-sectional	India	N: 376 Mean age: 39.8 Males: 143 (38%)	Chronic low back pain	3	14.1 ± 5.1	302 (80.32%)	This study found a negative relationship between vitamin D status and pain intensity, as well as a significant likelihood of vitamin D deficiency in the nonspecific CLBP group.

*NM=Not-mentioned.

Table (2): Risk of bias assessment using ROBINS-I

Study ID	Bias due to confounding	Bias in the selection of	Bias in the classification	Bias due to deviations from	Bias due to missing data	Bias in the measuremen	Bias in the selection of	Overall bias
Xie et al., 2024 [14]	Mod	Mod	Low	Low	Low	Low	Low	Low

Duan et al., 2020 [15]	Low	Low	Low	Low	Low	Mod	Low	Low
Kumar et al., 2020 [16]	Mod	Low	Mod	Mod	Low	Low	Low	Moderate
Overstreet et al., 2022 [17]	Mod	Mod	Low	Low	Low	Mod	Mod	Moderate
Ghani et al., 2023 [18]	Mod	Mod	Low	Low	Low	Mod	Low	Moderate
Hao-Wei et al., 2021 [19]	Low	Mod	Mod	Mod	Low	Mod	Low	Moderate
Wu et al., 2019 [20]	Mod	Mod	Low	Low	Low	Low	Mod	Moderate
Kumar Yadav et al., 2021 [21]	Crit	Mod	Low	Low	Mod	Low	Low	Critical

4. Discussion

This review reported that the prevalence of vitamin D deficiency ranged from 1.5% [20] to 82.3% [16] in patients with chronic pain. The prevalence of vitamin D deficiency ranged from 1.5% [20] to 82.3% [16] in patients with chronic pain. Lack of vitamin D has been linked in studies to an increased risk of experiencing pain across the body rather than just in one area [15, 17, 19, 21]. However, several studies found no connection between vitamin D levels and persistent pain, suggesting that vitamin D may not have an impact on the way people experience certain types of chronic pain, such as persistent lower back pain. Numerous studies found that many persons with chronic pain had insufficient vitamin D, suggesting a potential relationship but not proving causation. For instance, some studies revealed no correlation between vitamin D levels and osteoporosis or bone loss [14, 15, 16, 18, 20]. Chatterjee et al. found that there is currently moderate evidence linking low vitamin D to generalized chronic low back pain [22].

Zadro et al. stated that low back pain is linked to vitamin D deficiency; the correlation is higher in younger women and those with severe deficiency. There is conflicting evidence linking vitamin D levels to the severity of pain [23]. Wu ZhenQiang et al. also included 81 observational studies in a meta-analysis and found that low vitamin D levels are linked to persistent generalized discomfort, muscle soreness, and arthritis [24].

Gaining knowledge about how vitamin D deficiency affects pain intensity could help determine how vitamin D supplements might be used to treat low back pain. However, it is challenging to draw definitive conclusions on the impact of vitamin D in individuals who already have low back pain due to the significant heterogeneity among research examining the relationship between vitamin D and pain intensity.

Notably, it is suggested that vitamin D deficiency may produce chronic nonspecific pain through the disturbance of calcium homeostasis and the loss of anti-inflammatory, anti-apoptotic, or anti-fibrotic actions [25, 26]. These processes suggest that the body's tissues are the main source of chronic nonspecific pain. Despite their seeming intuitiveness, these pathways may not align with contemporary theories of chronic pain syndromes, including chronic nonspecific pain. The hypothesis that vitamin D shortage would exacerbate pain rather than lessen it has not yet been adequately investigated, despite the fact that it may interfere with the neuroimmunological mechanisms that underlie pain [27] by upsetting immune control [25, 26]. The dominant theories of chronic pain focus more on the nociceptive system's increased sensitivity [28], the role of non-nociceptive sensory inputs and associative learning [29], and cognitive mechanisms that de-emphasize ongoing tissue pathology or damage (with some exceptions, such as seronegative arthropathies) [30] and emphasize perceived threat to body tissue and behavioral processes that link fear of pain, activity avoidance, and catastrophizing [31].

Screening for and treating vitamin D deficiency could be a safe and affordable addition to chronic pain management. It may help improve outcomes for patients by reducing pain intensity in those who are deficient. Moreover, for groups more likely to have vitamin D deficiency, like older adults and people with little sunlight exposure, vitamin D supplementation could potentially act as a preventive strategy. However, more studies are required to validate its effectiveness in alleviating chronic pain symptoms. Healthcare providers should think about including vitamin D evaluations in holistic pain management strategies, especially for patients experiencing ongoing, widespread pain issues.

5. Strengths and limitations

This systematic review brings together various studies from different countries, giving us a comprehensive understanding of the possible connection between vitamin D and chronic pain in various populations. By including studies that look at both observational and interventional results, we gain a deeper insight into whether vitamin D supplementation could be beneficial as a treatment. The review also emphasizes the importance of demographic and inflammatory factors in influencing the relationship between vitamin D deficiency and chronic pain, suggesting important areas for future research.

One major limitation of this review is the inconsistency across studies in how pain was measured, how vitamin D deficiency was defined, and the differences in demographics. Many studies were cross-sectional, which means we can't determine cause and effect. Also, factors that could influence both vitamin D levels and pain experiences, such as physical activity levels, other health conditions, and nutrition, were not consistently controlled in all studies. This may affect the results. Additionally, the lack of standardized thresholds for defining vitamin D deficiency makes it even more difficult to interpret the findings since different definitions could impact how comparable the results are.

6. Conclusion

This review highlights a potential link between vitamin D deficiency and chronic pain, especially in cases of widespread musculoskeletal pain. While it's not definitively proven that vitamin D deficiency causes this pain, it seems to make it worse for some groups of people, possibly by triggering inflammation. Checking vitamin D levels in patients with chronic pain could be a helpful part of their treatment plan, especially for those who are at risk of having low vitamin D. Future studies should aim to conduct thorough and long-term research to better understand how vitamin D deficiency and chronic pain are connected and evaluate the effectiveness of supplementation as a treatment option.

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