

**FULL PAPER**

# Role of vitamin D on knee osteoarthritis pain: a systematic review

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Vitamin D3 (Cholecalciferol) has the chemical formula of (C<sub>27</sub>H<sub>44</sub>O), molecular weight (384.6), exact mass (384.339216023), and mono-isotopic mass (384.339216023). The researchers conducted this study to examine the role of Vitamin D on the knee osteoarthritis pain. The original published articles (interventional or correlational) aimed to investigate the role of vitamin D on Knee OA pain. The search was done by using the keywords "pain, knee osteoarthritis, osteoarthritis, Vitamin D, Vitamin D3, knee, Cholecalciferol, and vitamin D deficiency" and these mentioned keywords were used by "OR" and "AND" search methods. Regarding gray texts, all related articles and their references were reviewed. Based on the findings of 15 articles, there was no relationship between vitamin D and pain in 2 articles, pain was lower in the high vitamin D group (No significance < 0.05) in 1 article, and increasing vitamin D reduced pain in 12 articles. In 9 articles, the search method was Randomized Trial, and in 6 ones, it was cross-sectional. According to the findings, although in most reviewed articles, vitamin D led to the reduction of Knee OA pain, in some of them, the difference in pain reduction between the group receiving vitamin D and the placebo group was not significant. Therefore, acceptable evidence for its effectiveness is not available and it is necessary to conduct more studies in this field.

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**KEYWORDS**

Cholecalciferol; knee osteoarthritis; pain.

**Introduction**

Vitamin D3 (Cholecalciferol) has the chemical formula of (C<sub>27</sub>H<sub>44</sub>O), molecular weight (384.6), exact mass (384.339216023), mono-isotopic mass (384.339216023), and chemical structure as displayed in Figure 1. Synonyms used for vitamin D include cholecalciferol, Calcilol, Colecalciferol, Duphafral D3 1000, Vi-De3, Oleovitamin D3, and others. Cholecalciferol, in terms of pharmaceutical category, includes vitamins, and in terms of formulation, is oral solid and liquid. Also, its

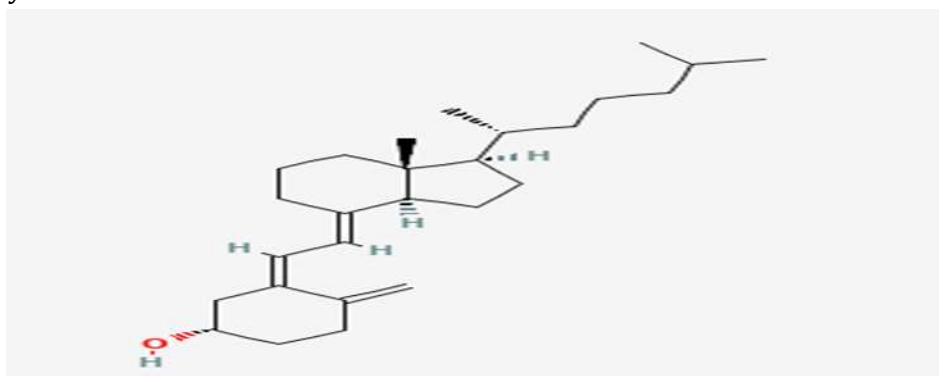
solid form is 400 IU, 1000 IU, and its liquid type is Liquid: 400 IU per mL [1].

It is initially necessary to hydroxylate vitamin D to 25-hydroxyvitamin D during changes in the liver, and then convert it into 25-hydroxyvitamin D in the kidney [2-4]. In vitamin D, its activity is done through Vitamin D receptor (VDR). The VDR gene has different types such as BsmI (rs1544410) and FokI (rs2228570 [5]. The level of variables in the blood and biochemical metabolisms carried out by drugs have a direct effect on the clinical pain status of patients [6-8]. For example, with

the metabolism carried out for vitamin D in the liver, and then the kidney, VDR can lead to biological changes in the pain status of patients. In the conducted studies, the relationship between 25(OH)D and chronic pain (CP) has been confirmed, so that low concentration of vitamin D has led to CP in patients [9-11]. Vitamin D deficiency exists in developing or even developed countries and can lead to pain in patients with rheumatoid arthritis, osteoporosis, osteoarthritis, arthralgia, back pain, and soft tissue rheumatism [12,13].

Pain is a non-desired status that may appear in all age ranges of patients from infancy to old ages, diseases with different diagnoses, including patients with diabetic neuropathy and those with CP head trauma

[14-16]. Knee osteoarthritis (Knee OA) is one of the diseases associated with pain [17,18]. Knee OA causes inflammation, pain, capsular ligament laxity, weakness and muscle atrophy, and as a result, the dysfunction of the joint receptors leads to increase additional forces on the joint, and finally aggravates the complication [19-21]. The functional and motor independence of the patient has an impact on the quality of patient care, which is why measures to increase functional and motor independence are necessary, including pain reduction that can lead to a decline in disability and an increase in the person's disability [22]. The aim of study was to investigate the role of vitamin D on the knee osteoarthritis pain.



**FIGURE 1** Chemical backbone of vitamin D

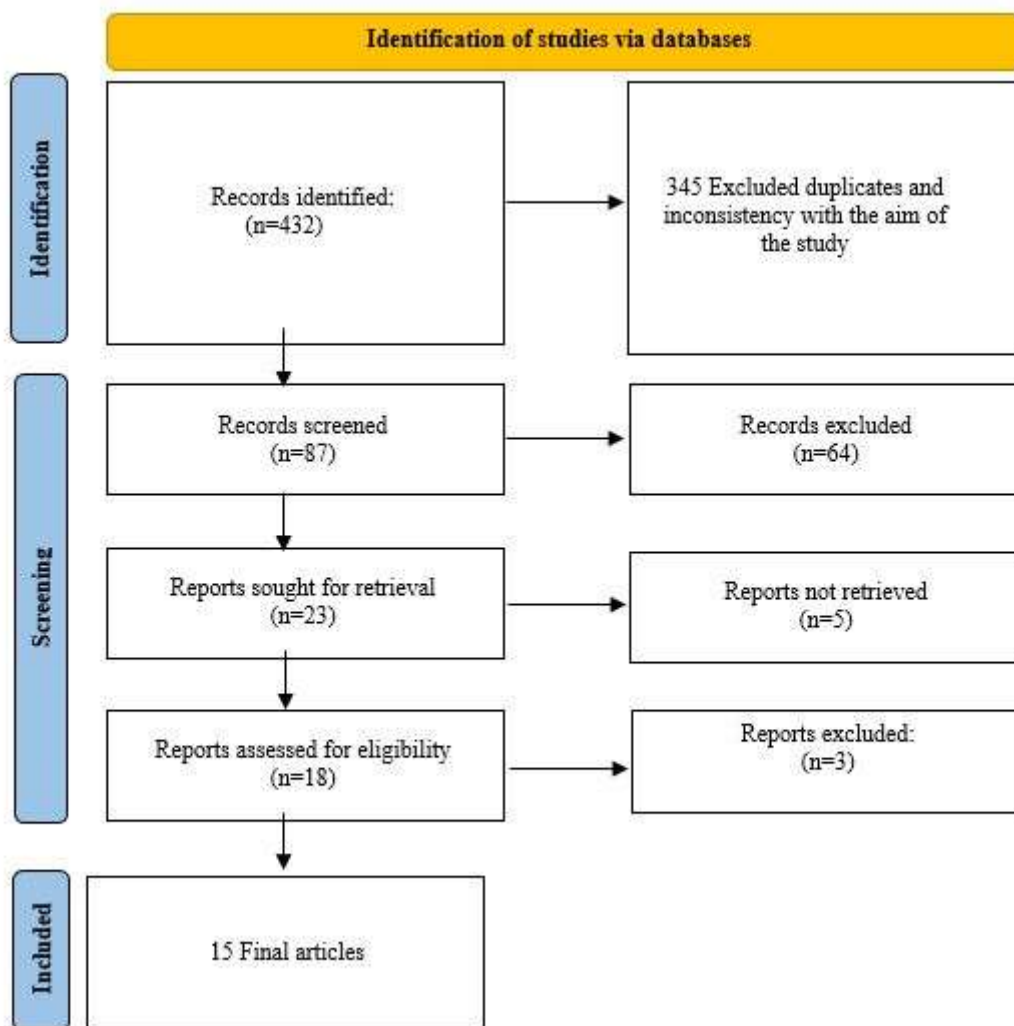
## Methods

The original published articles (interventional or correlational) aimed to consider the role of vitamin D on knee OA pain were reviewed and, in this study, the search and screening strategies were selected based on PRISMA guidelines [44].

To access the related studies, the search strategy was in PubMed, Scopus, Science Direct, ISI, and Google Scholar scientific search engine, which was searched until the beginning of 2022. The search was done using the keywords "pain, knee osteoarthritis, osteoarthritis, Vitamin D, Vitamin D3, knee, Cholecalciferol, and vitamin D deficiency" and these mentioned keywords were used by "OR"

and "AND" search methods. Regarding to gray texts, all related articles and their references were reviewed.

First, searching and retrieving articles were carried out and two researchers carefully examined the articles. Then, the titles and abstracts of the retrieved articles and the articles that met the inclusion criteria were reviewed. In case of disagreement, the obtained information was re-evaluated by discussion between the authors, retrieving the information, and re-reading the articles. Next, the extracted information was entered into the checklist of the researcher (including the type of study, country, etc.), that is listed Table 1, and qualitative findings were analyzed.



**FIGURE 2** Flowchart of the current systematic review

## Results

According to the findings, 432 articles were extracted in the initial search, and finally 14 articles entered the systematic review stage. In all reviewed articles, vitamin D reduced the pain of knee OA patients (Figure 2). Based on the findings of 15 articles, there was no

relationship between vitamin D and pain in 2 articles, pain was lower in the high vitamin D group (No significance  $< 0.05$ ) in 1 article, and increasing vitamin D reduced pain in 12 articles. In 9 articles, the article method was Randomized Trial and in 6 ones, it was cross-sectional (Table 1).

**TABLE 1** The main results of the articles

| No. | Author                               | type of study    | Country       | Study design | Scale               | N                              | Mean Age (SD)                                  | Intervention         |                       | Pain status   |
|-----|--------------------------------------|------------------|---------------|--------------|---------------------|--------------------------------|--|----------------------|-----------------------|---|
|     |                                      |                  |               |              |                     |                                |  | Drug dose            | Duration of follow-up |   |
| 1   | Manoy <i>et al.</i> (2017) [23]      | Randomezed Trial | Thailand      | Knee OA      | VAS (0-10)          | 175                            | 64.58(0.55)                                    | 40,000 IU vitamin D2 | 6 months              | At the beginning of the study, M(SD) of the patients' pain was equal to 3.96(0.17) and 6 months after the intervention, it was equal to 3.44(0.17), (P=0.002).  |
| 2   | MacFarlane <i>et al.</i> (2020) [24] | Randomezed Trial | United States | Chronic KP   | WOM AC pain (0-500) | 1398                           | 67.7 (6.9)                                     | 800 IU/day           | -                     | No effect.  |
| 3   | Tu <i>et al.</i> (2017) [25]         | Randomezed Trial | Australia     | Knee OA      | WOM AC pain (0-500) | vitamin D: 209<br>Placebo: 204 | Vitamin D: 63.55(6.88)<br>Placebo: 62.85(7.22) | -                    | -                     | M(SD) of pain in the group with vitamin D intake was equal to 137.88(88.82) and in the group without vitamin D intake, it was equal to 134.74(83.42), (P<0.71).<br>Before the intervention, the M(SD) of pain in the vitamin D group was 10.94(2.63) and in the placebo group, it was 10.64(2.82) (p=0.58). While after the intervention and after a one-year follow-up, the difference between the two groups was equal to 1.70 (2.28 to 1.12) - with a significant level of p<0.001, which indicates the effect of vitamin D. |
| 4   | Sanghi <i>et al.</i> (2013) [26]     | Randomezed Trial | India         | Knee OA      | WOM AC-pain (0-20)  | vitamin D: 52<br>Placebo: 51   | Vitamin D: 53.24(9.64)<br>Placebo: 53.00(7.44) | Oral vitamin D       | 1-year                | M(SD) of pain in the group with vitamin D intake was equal to 137.88(88.82) and in the group without vitamin D intake, it was equal to 134.74(83.42), (P<0.71).<br>Before the intervention, the M(SD) of pain in the vitamin D group was 10.94(2.63) and in the placebo group, it was 10.64(2.82) (p=0.58). While after the intervention and after a one-year follow-up, the difference between the two groups was equal to 1.70 (2.28 to 1.12) - with a significant level of p<0.001, which indicates the effect of vitamin D. |

|   |                                     |                  |               |         |                                  |                                |  |                         |            |   |
|---|-------------------------------------|------------------|---------------|---------|----------------------------------|--------------------------------|--|-------------------------|------------|---|
| 5 | Heidari <i>et al.</i> (2015) [27]   | cross-sectional  | Iran          | Knee OA | WOM AC-pain (0-16)<br>VAS (0-10) | 67                             | 50(6.6)                                    | 50.000 IU               | Two months | Before the intervention, the M(SD) of the patients' pain by using the WOMAC scale was equal to 9.16(1.84) and after the intervention, it decreased to 2.04(0.97) (P<0.005). In addition, according to the VAS instrument, the M(SD) status of pain before the intervention was equal to 39.3(6.1) and after the intervention was equal to 13.2(4.0) (P<0.001). In the vitamin D group, the M(SD) status of pain before the intervention was 137.9(88.8) and 24 months later, it was 87(90.1) (P<0.05), while in the placebo group, it was 134.7(83.4) before the intervention and 24 months after the intervention, it was equal to 97.2 (87.5) (P=0.10). |
| 6 | Jin <i>et al.</i> (2016) [28]       | Randomized Trial | China         | Knee OA | WOM AC pain (0-500)              | Vitamin D: 209<br>Placebo: 204 | Vitamin D: 63.5(6.9)<br>Placebo: 62.9(7.2) | 50 000 IU of vitamin D3 | 24 months  | No effect.  |
| 7 | Arden <i>et al.</i> (2016) [29]     | Randomized Trial | London        | Knee OA | WOM AC pain (0-100)              | Vitamin D: 237<br>Placebo: 237 | Vitamin D: 64(8)<br>Placebo: 64(8)         | 800IU of oral           | 12 months  | No effect.  |
| 8 | McAlindon <i>et al.</i> (2013) [30] | Randomized Trial | United States | Knee OA | WOM AC pain (0-100)              | Vitamin D: 73<br>Placebo: 73   | Vitamin D: 61.8(7.7)<br>Placebo: 63(9.3)   | 2000 IU daily           | 2-year     | Before the intervention, the M(SD) of pain in the vitamin D group was 6.9(3.8) and the placebo group was 5.8(3.4), and after  |

|    |                                    |                  |           |         |                     |  |  |   |          |  |
|----|------------------------------------|------------------|-----------|---------|---------------------|--|--|---|----------|--|
| 9  | Velangi <i>et al.</i> (2019) [31]  | Randomized Trial | India     | Knee OA | VAS (40-70)         | Vitamin D: 50<br>Vitamin D3 + VCNO supplementation: 50 | 30-65yrs                                   | Oral and intravenous vitamin D was given to the patients. | 12 weeks | the intervention, the pain level of both groups decreased, but the difference between them was not significant. (P>0.05).<br><br>The pain level in the vitamin D group was much lower than the group receiving Vitamin D3 + Virgin Coconut oil (VCNO) supplementation.   |
| 10 | Perry <i>et al.</i> (2019) [32]    | Randomized Trial | UK        | Knee OA | WOM AC pain (0-100) | Vitamin D: 24<br>Placebo: 26                           | vitamin D: 63(5.8)<br>Placebo: 63.6(7.2)   | 800 IU daily  | 2-year   | Before the intervention, the M(SD) of pain in the vitamin D group was 29.4 (15.6) and the placebo group was 34.3 (19.5) (the pain in the vitamin D group was lower than the placebo group before the intervention). It should be noted that the pain status after the intervention was not investigated. Vitamin D levels were higher in patients with lower pain. |
| 11 | Başkan <i>et al.</i> (2018) [33]   | Cross-sectional  | Turkey    | Knee OA | VAS (0-10)          | 107  | 63.0(9.6)                                  | -   | -        | M(SD) of pain in adequate vitamins: 99.4 (93.8) and vitamin deficiency: 485.7 (440.7)  |
| 12 | Levinger <i>et al.</i> (2017) [46] | Cross-sectional  | Australia | Knee OA | WOM AC pain (0-500) | 24   | 68.6(6.2)                                  | -   | -        | The pain score in the group with vitamin D deficiency was 3(0-8) in resting status and 7(2-10) in motion status, while in the  |
| 13 | Alkan <i>et al.</i> (2020) [34]    | Cross-sectional  | Turkey    | Knee OA | VAS (0-10)          | 81   | Group 1: 68.1(1.48)<br>Group 2: 67.8(1.30) | -   | -        |  |

|    |  |                 |        |         |                   |     |  |   |  |   |
|----|--|-----------------|--------|---------|-------------------|-----|--|---|--|---|
|    |  |                 |        |         |                   |     |  |   | group with sufficient vitamin D, this value was 2(0-5), and also 6(3-9) (P<0.05). In addition, WOMAC-Pain score was 12(7-18) in the group with vitamin deficiency and 8(2-17) in the group without vitamin deficiency (P<0.001). |   |
| 14 | Ana Alabajos-Cea <i>et al.</i> (2021) [45] | Cross-sectional | Spain  | Knee OA | VAS (0-10)        | 96  | Group 1:<br>52.36<br>(5.02)<br>Group 2:<br>50.72<br>(6.87) | - | -  | Vitamin D levels were higher in patients with lower pain. |
| 15 | Namutebi <i>et al.</i> (2021) [47]         | Cross-sectional | Uganda | Knee OA | WOMAC pain (0-96) | 107 | ><br>83(77.6%)<br><<br>24(22.4%)                           | - | -  | Vitamin D levels were higher in patients with lower pain. |

## Discussion

The challenges of chronic diseases such as lifestyle should be prioritized in research [35, 36]. Knee OA is known as one of the chronic diseases, especially in the elderly, which causes pain [37,38]. In this review study, the reviewed articles examined the role of Cholecalciferol on the knee OA pain.

Vitamin D reduced pain in the study of MacFarlane *et al.* [24] in 2020 and in the United States, in the study of Tu *et al.* [25] in 2017 and in Australia, in the study of Arden *et al.* [29] in 2016 in London, in the study of McAlindon *et al.* [30] in 2013 in the United States, vitamin D reduced pain. However, compared with the placebo group or other groups, this reduction was not significant, yet in other studies, this reduction was significant. In the meta-analysis study of Diao *et al.*, it was shown that in 4 clinical trials examined, vitamin D had little effect on reducing the pain

of Knee OA patients [39]. In addition, in a study conducted by Hussain *et al.*, including the review of the results of 5 articles, except one article, vitamin D did not have any effects on reducing knee OA pain [40], which is consistent with the results of some articles reviewed in this systematic review study on the low effect of vitamin D on pain reduction in knee OA patients.

In articles reviewed in this review study, it was revealed that vitamin D reduces the pain of Knee OA patients so that in the meta-analysis study by Zhao *et al.* (2021), which examined 6 articles, the pain status of Knee OA pain was reduced after the use of vitamin D [41]. In Hatfi *et al.*'s study that *Duloxetine* reduces the pain of spinal cord injuries (SCIs) patients, six articles were included in the systematic review, which showed that *Duloxetine* reduces the pain of SCIs patients [42]. In a review study by Zarrati *et al.* (2022), it was indicated that vitamin D caused to



reduce the pain of cancer patients [43] which is consistent with the results of some studies reviewed in this review study regarding the effect of vitamin D on the reduction of knee OA pain. Hence, the use of vitamin D is recommended.

## Conclusion

According to the findings, although in most of the reviewed articles, vitamin D led to the reduction of Knee OA pain, but in some of them, the difference in pain reduction between the group receiving vitamin D and the placebo group was not significant. Therefore, the acceptable evidence for its effectiveness is not available and it is necessary to conduct more studies in this field.

## Acknowledgments

The authors gratefully thank Al-Nisour University College, University of Mosul/College of Pharmacy, and University of Baghdad/College of Pharmacy for providing facilities that improved the quality of this work.

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**How to cite this article:** Ali Karbasfrushan, Hosein Karimiyarandi\*. Role of vitamin D on knee osteoarthritis pain: a systematic review. *Eurasian Chemical Communications*, 2022, 4(12), 1241-1250. **Link:** [http://www.echemcom.com/article\\_153675.html](http://www.echemcom.com/article_153675.html)