PRINCIPLES AND PRACTICE OF CLINICAL RESEARCH
A Global Journal of Clinical Research

Vitamin D Supplementation for Uterine Fibroids: What Does the Evidence Say? A Systematic Review of Primary and Secondary Outcomes

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Abstract

Introduction: *Uterine fibroids affect millions of women, and non-surgical management options are limited. Vitamin D, with its potential role in cell growth regulation, may be a promising non-surgical option.*
Objective: *This study reviews human studies from 2018 to 2023 to assess how vitamin D affects uterine fibroids (UFs). It aims to identify primary and secondary outcomes related to vitamin D's impact on UFs and stresses the importance of a core outcome set (COS) in fibroid research.*
Methods: *A comprehensive search of PubMed, MEDLINE, Google Scholar, and the Cochrane Library used specific keywords related to vitamin D, uterine fibroids/myoma/leiomyoma, and primary and secondary outcomes. The literature search was limited to English-language publications and studies published before October 30, 2023. The review follows the PRISMA guidelines. Quality assessment was performed.*
Results: *Eight relevant studies with a total of 565 participants were included. In all studies, the primary outcome focused on vitamin D's effect on the volume/size of UFs. The most reported secondary outcomes included changes in vitamin D levels, pelvic pain or pressure, fatigue and menstrual bleeding, quality of life, and fibroids. The results show that vitamin D supplementation may have potential benefits for uterine fibroids, though the evidence remains inconclusive. While some high-quality studies reported reductions in fibroid size, others did not observe significant impacts. However, several studies have shown improvements in secondary outcomes, such as pain and quality of life.*
Conclusion: *The mixed results highlight the need for more rigorous, standardized research using a core outcome set (COS). Future well-designed RCTs are necessary to provide definitive answers on the effectiveness of vitamin D supplementation for managing UFs.*

Introduction

Uterine fibroids (UFs), also known as leiomyomas, represent the most prevalent benign tumors affecting the female reproductive system, with an estimated prevalence of 70-80% among women by the age of 50 (Alkhrait et al., 2023). These tumors can give rise to a range of debilitating symptoms, including heavy menstrual bleeding, pelvic pain and discomfort, and, in some cases, even impaired fertility (Alkhrait et al., 2023). Notably, the global burden of UFs appears to be on the rise, with women of African descent disproportionately affected by this condition (Sutton et al., 2021). The substantial healthcare costs associated with UFs are well-documented, with annual expenditures in the United States alone estimated at $34.4 billion and significant indirect societal costs (Alkhrait et al., 2023).

Emerging epidemiological evidence has reported a significant association between vitamin D deficiency and the presence of UFs (Vergara et al., 2021). Furthermore, in vitro studies have shown that vitamin D can effectively inhibit UF growth by targeting critical pathways regulating cellular processes such as proliferation, extracellular matrix remodeling, DNA repair, signaling, and programmed cell death (Vergara et al., 2021). Building on this insight, a recent review by Ciebiera et al. (2020) has proposed preliminary clinical guidance regarding the measurement of 25-hydroxyvitamin D levels in women with UFs or at high risk, suggesting that achieving sufficient vita-

*Corresponding author: iana.malasevscaia@gmail.com
Received: January 28, 2024 **Accepted:** September 15, 2024
Published: November 28, 2024
Editor: Felipe Fregni
Reviewers: Karen Mori, Gabriel Vallejos, Laura Alvarez, Vinicius Aniceto
Keywords: vitamin D, uterine fibroids, primary outcomes, secondary outcomes
DOI: https://doi.org/10.21801/ppcrj.2024.103.3

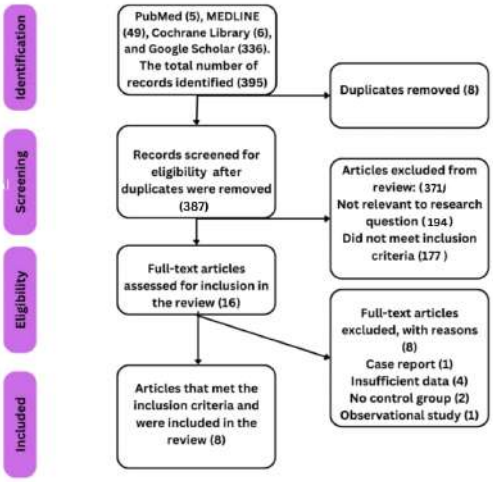

Figure 1: *PRISMA flow diagram.*

min D status may be of potential importance in the management of this common gynecological condition. These findings underscore the clinical relevance of assessing vitamin D levels in the context of UFs and warrant further investigation into the therapeutic utility of vitamin D supplementation.

Given the substantial impact of UFs and the limitations of current treatment options, exploring alternative therapies such as vitamin D supplementation, which may offer a noninvasive and safe approach to managing this prevalent condition, is crucial. This systematic review aims to comprehensively evaluate the current evidence of the impact of vitamin D supplementation on uterine fibroids. This review will investigate the primary and secondary outcomes reported in existing studies to assess the potential benefits of vitamin D in managing this prevalent condition.

Materials and Methods

A comprehensive search was conducted across electronic databases, including PubMed, MEDLINE, Google Scholar, and the Cochrane Library (see Figure 1 for the PRISMA flow diagram). The search strategy utilized keywords related to vitamin D, uterine fibroids (including synonyms like myoma and leiomyoma), randomized controlled trials (RCTs), controlled clinical trials (CCTs), pilot studies, primary outcomes, and secondary outcomes. The search was limited to English-language publications between 2018 and October 30, 2023, to ensure that recent findings were captured.

Studies were included if they investigated the effects of vitamin D supplementation on uterine fibroids in human participants. The review included studies with controlled designs, encompassing RCTs, CCTs, and pilot studies within these categories (Table 3). Studies were required to report primary or secondary outcomes relevant to uterine fibroids, such as changes in fibroid size/volume, bleeding symptoms, or pain.

Articles identified through the initial search were imported into the Rayyan systematic review software to eliminate duplicate records (Ouzani et al., 2016). Titles and abstracts were screened based on the established inclusion and exclusion criteria. For potentially relevant studies, full-text articles were retrieved for further evaluation

Appropriate tools were employed to assess the risk of bias in the included studies. For studies with a randomized controlled design (RCTs), the Cochrane risk-of-bias tool for randomized trials (RoB 2) (Table 1) was used (Sterne et al., 2019. For non-randomized studies (CCTs and pilot studies), the ROBINS-I tool was employed (Table 2) (Sterne et al., 2016).

Results

An initial search yielded 395 records, subsequently consolidated into 387 distinct articles after removing duplicates. A comprehensive screening process based on titles and abstracts led to the selection of 16 articles for full-text review. Ultimately, eight studies met the inclusion criteria and were incorporated into this review. The methodological landscape of the included studies was diverse, encompassing two RCTs with a low risk of bias, as assessed by the Cochrane tool, and six CCTs, including three pilot studies, which were classified as having a moderate risk of bias (Tables 1 & 2).

Authors/Year	D1	D2	D3	D4	D5	Overall
Hajhashemi et al., (2019)	+	+	+	+	+	+
Arjeh et al., (2020)	+	+	+	+	+	+

Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., ... Higgins, J. P. T. (2019). RoB 2: A revised tool for assessing risk of bias in randomized trials. BMJ, 366, l4898.

Domain 1: Risk of bias arising from the randomization process (D1)
Domain 2: Risk of bias due to deviations from the intended interventions (D2)
Domain 3: Risk of bias due to missing outcome data (D3)
Domain 4: Risk of bias in the measurement of the outcome (D4)
Domain 5: Risk of bias in the selection of the reported result (D5)

Table 1: *The risk of bias domains assessment using Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2).*

Authors/ Year	Confounding	Selection bias	Classification of intervention	Intended intervention	Missing data	Measurement of outcomes	Reported results	Overall
Xess, S., & Sahu, J. (2020)	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Tabrizian et al., (2021)	Moderate	Moderate	Low	Low	Moderate	Moderate	Low	Moderate
Miriello et al., (2021)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Porcaro G., & Angelozzi P., (2021)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Porcaro et al., (2020)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Orive et al., (2023)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate

Sterne, J. A. C., Hernán, M. A., Reeves, B. C., Savović, J., Berkman, N. D., Viswanathan, M., ... Higgins, J. P. T. (2016). ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. BMJ, 355, i4919. doi:10.1136/bmj.i4919

Table 2: *The risk of bias in non-randomized studies - of interventions (ROBINS-I) assessment.*

A total of 565 participants from multiple controlled clinical trials were included in this analysis. Study sample sizes ranged from 20 to 137 participants, with most trials enrolling between 30 and 137 individuals. Mean participant age across studies varied from 31.26 to 45.0 years. Baseline 25-hydroxyvitamin D (25(OH)D) levels were consistently low across studies, ranging from 12.2 to 24.8 ng/mL. Uterine fibroid (UF) characteristics at baseline also demonstrated variability, with the most extensive diameter measurements from 10 mm to 60.31 mm and volume from 8.2 to 67.07 cm^3 (Tables 3, 4, 5).

Vitamin D supplementation regimens varied widely across studies. Doses ranged from 50,000 IU every two weeks for ten weeks to 60,000 IU once weekly for twelve weeks, followed by a maintenance dose of 2,000 IU weekly for a year. Some trials incorporated additional supplements, such as epigallocatechin gallate (EGCG) and vitamin B6, in conjunction with vitamin D supplementation. Control groups received either a placebo or no intervention. The primary outcome measure across all studies was the change in uterine fibroid size, assessed by either diameter or volume. Secondary outcomes commonly evaluated included serum 25(OH)D levels, parathyroid hormone, and calcium concentrations, symptoms associated with uterine fibroids (e.g., heavy menstrual bleeding, pelvic pain, quality of life), and other laboratory markers such as liver enzymes and creatinine (Table 3, 4, 5).

The primary outcome, a change in fibroid size, yielded mixed results. Hajhasshemi et al. (2019) and Miriello et al. (2021), two RCTs with a low risk of bias, reported significant reductions in fibroid size with vitamin D supplementation compared to the control group ($p < 0.05$). However, CCT studies by Arjeh et al. (2020) and Tabrizian et al. (2021) did not observe a statistically significant difference in fibroid size between groups ($p > 0.05$). Interestingly, Xess and Sahu (2020) found no substantial change in fibroid size in the intervention group, but the control group showed a significant increase ($p < 0.001$).

Discussion

This systematic review encompassed eight studies investigating the potential efficacy of vitamin D supplementation in managing uterine fibroids. The study included two RCTs and six CCTs. (Figure 3). While the studies explored the potential of vitamin D for fibroids, the evidence regarding its impact remains inconclusive.

The primary outcome, a change in fibroid size, yielded mixed results. This discrepancy in the primary outcome results could be attributed to several factors. Firstly, the study designs may have played a role. With their rigorous methodology and randomization, the RCTs could be better controlled for potential confounding factors compared to the CCTs. Additionally, the sample sizes of the RCTs were relatively small, which could limit the generalizability of their findings.

Secondly, the baseline characteristics of the study populations may have influenced the outcomes. The

Study /Authors/ Year	Study design	Nr. of participants, per group	Participants' characteristics	Intervention	Primary outcome(s)	Secondary outcome(s)
Hajhashemi et al., (2019)	RCT	(70) 35/35 intervention/ control group	Mean age(years), intervention 40.58±4.26 vs control 40.6±4.08, 25-hydroxyvitamin D3 levels (ng/ml) 16.82±2.22 vs 16.77±2.32, Leiomyoma size (mm) 59.73±13.51 vs 60.31±11.3	Vit D 50,000 IU every 2 weeks, for 10 weeks Control/Placebo	UFs size	The 25-OH-D3 level
Arjeh et al., (2020)	RCT	(60) 30/30 each group (study/ control)	Mean age (years), Intervention 31.26 ±5.67 vs control 33.14 ± 6.16, The largest diameter of UF greater than 10 mm Numbers of UFs less than four Serum [25(OH)D] level less than 30 ng/mL.	Vit. D 50,000 IU/weekly 12 weeks Control/Placebo	UFs volume	1. The 25-OH-D3 level 2. Parathyroid hormone level. 3. Calcium level
Tabrizian et al., (2021)	CCT	(137) 52 in the insufficiency group 85 in the deficiency group	Mean age, insufficiency group 41.2±6.53 vs deficiency group 39.4±6.6 Single myoma (all types) Baseline vitamin D 24.8±2.8 vs 12.2±3.8	Deficiency group: 50,000 IU/week for 12 weeks) of vitD Baseline vitamin D 24.8±2.8 vs 12.2±3.8 Control group/ Insufficiency group: supplementation of 1000 IU/ day for 12 weeks	UFs size	The 25-OH-D3 level
Xess, S., & Sahu, J. (2020)	CCT	(130) 60 study group / 50 "control group"	Mean age (years), study group 45±5.0, vs "control group" 45±3.7 Mean 25-OH-D3 level at inclusion (ng/mL), 19.9, vs 21,4 Mean diameter of UFs at inclusion (mm) 25.7 vs 23.1 Mean volume (cm3) 8.2 vs 11.4	60,000 IU of vitamin D once per week for 12 weeks, followed by maintenance therapy of 2000 IU weekly for a year Control/ Same Tx, non-compliant with Tx.	UFs volume UFs diameter	1. The 25-OH-D3 level 2. "Progression to extensive disease" (with the development of one or more fibroids >50 mm) or by a significant worsening of fibroids related symptoms
Miriello et al., (2021)	CCT	(95) 41 study/54 control	Mean age, intervention group 37.78 ± 2.1 vs 38.96 ± 2.4 control group At least one myoma with a diameter <4 cm Myomas' volume (mean/SD) cm³ 20.55 ± 1.16 in study group, vs 21.31 ± 1.91 in control group	By oral route one tablet of 25 µg vitamin D + 150 mg EGCG + 5 mg vitamin B6, twice a day for 4 months. Control/No Tx	UFs volume	1. Myoma's vascularization (the variation of myomas color score) 2. Heavy menstrual bleeding 3. Pelvic pain 4. Number of total myomas 5. Women's health and quality of life
Porcaro G., & Angeloni P., (2021)	Pilot study/ CCT	(45) 22 study/23 control	Mean age study group 37.86 ± 4.86, vs control 37.33 ± 6.71 Volume UFs (cm3): study group 10.73 ± 5.52 vs 10.21 ± 5.83 control Mean n° UFs 1.55 ± 0.74 vs 1.29 ± 0.64	Twice a day with 150 mg EGCG, 25 µg vitamin D and 5 mg vitamin B6, for 4 months Control/ No Tx	UFs size and numbers	1.Reduction of menstrual blood loss 2. Fatigue 3. Feeling of pressure in the pelvic area. 4. The mean Hb 5. Blood pressure
Porcaro et al., (2020)	Pilot study/ CCT	(30) 15 study/15 control	Mean age study group 37.27 ± 1.13 vs 37.67 ± 1.71 control group Mean n° myomas: 1.53 ± 0.19 vs 1.40 ± 0.19 Volume of myomas cm3: 10.84 ± 1.16 vs 10.17 ± 1.43	25 µg vitamin D + 150 mg EGCG + 5 mg vitamin B6 twice a day for 4 months Control/ No Tx	Change o UFs volume	1. Variation of the number of myomas 2. Distress by bleeding during the menstrual period 3. Pelvic pain/pressure 4. Sense of fatigue 5. Quality of life 6. Severity of symptoms
Orive et al., (2023)	Pilot study/ CCT	(20) study group 6/ control 14	Age: under 45 years old, age (control 40.57 ± 2.76 vs. 38.75 ± 4.92, study group) UFs (cm3) size (control 67.07 ± 20.68 vs. 56.17 ± 12.56 study group) Hypovitaminosis D [25(OH)D levels < 30 ng/mL), Vitamin D levels (control 18.57 ± 7.47 vs. 23.37 ± 37.29 study group)	vitamin D for 6 months (25000 IU/2 weeks) Control/No Tx	UFs size	1. Serum levels of (25(OH)D) 2. Serum calcium 3. Serum AST, ALT, bilirubin 4. Serum creatinine

Abbreviation: (RCT: Randomized Controlled Trial, CCT: Controlled Clinical Trial, UF/s: Uterine fibroid/s, 25(OH)D:25-hydroxyvitamin D3, AST: aspartate transaminase, ALT: alanine transaminase, Hb: hemoglobin, Tx: treatment, cm3: cubic centimeter, N°: number, EGCG: epigallocatechin gallate, IU: international unit, SD: Standard deviation, vs: versus).

Table 3: *Study details and primary and secondary outcome characteristics.*

Authors/Year of publication	Primary outcome results for study group	Primary outcome results for control group
Hajhashemi et al., (2019)	**UF size** (mm), before 59.73±13.51, after Tx 52.58±13.72, p-value <0.001	UF **size** (mm), before Tx 60.31±11.3, after 61.11±11.16, p-value 0.375
Arjeh et al., (2020)	**The largest UF volume** at baseline and after Tx: 22.88± 5.72 vs. 22.16 ± 6.18, p-value 0.085	**The largest UF volume** at baseline and after Tx: 22.51 ± 5.31 vs. 25.05 ± 6.25, p-value 0.001
Tabrizian et al., (2021)	**The UF size** (deficiency group): a 2.4% reduction in size, (p=0.664)	**The UF size** (insufficiency group): a 3.8% decrease in size after intervention, (p=0.148)
Xess, S., & Sahu, J. (2020)	**UFs volume**, cm3, before Tx., 8.2 (2.7-30.5) and after Tx 8.2 (2.1-28.5), p-value 0.63 UFs diameter(mm) 20 (17.3-38.8) vs. 20 (15.8-35.8), p-value 0.63	**UFs volume**, cm3, before Tx., 8.2 (4.2-21.4), after Tx 11.4 (5.5-22.3), p-value < 0.001 UFs diameter (mm) 25 (20-34.5) vs. 28 (22-35) p =value <0.001
Miriello et al., (2021)	UFs' **total volume** significantly decreased by 37.9% in the (from a mean value of 20.55 cm^3 to 12.65 cm^3, p-value <0.001)	**UFs' total volume** increased by 5.5%, from 21.31 ± 1.91, to 22.5 ± 2.11 cm^3, p – value 0.83
Porcaro G., & Angelozzi P., (2021)	**UFs size** (from 10.73 ± 5.52 cm3 at baseline to 7.98 ± 4.00 cm3 after Tx; p < 0.0001) **Mean n°** UFs: 1.55 ± 0.74 vs. 1.55 ± 0.74	**UFs size** (from 10.21 ± 5.83 cm3 at baseline to 10.62 ± 6.28 cm3 at the end of the study; p= 0.8076 **Mean n° Ufs:** 1.29 ± 0.64 vs. 1.33 ± 0.80
Porcaro et al., (2020)	Significant reduction in UF **volume** (from 10.84 ± 1.16 cm3 at baseline to 8.04 ± 0.85 cm3 (reduction in the volume of myomas (by 34.7%)) after Tx, p < 0.0001)	The **volume** significantly fluctuated from 10.17 ± 1.43 cm3 at T0, to 10.94 ± 1.50 cm3, (an increase in tumor size by (6.9%)) after 4 month-period observation (p < 0.001)
Orive et al., (2023)	**UF size:** a slight decrease in UFs size (-5.84 ± 2.14 %, p = 0.15)	**UF size:** a significant increase in UFs size (17.3 ± 14.31%, p = 0.0005)

Note: Values are presented as mean ± standard deviation.
Abbreviations: (UF/UFs: Uterine fibroid/s, Tx: Treatment, 25(OH)D: 25-hydroxyvitamin D3, Hb: Hemoglobin, AST: Aspartate transaminase, ALT: Alanine transaminase).

Table 4: *Summary of primary outcomes by groups.*

Authors/Year of publication	Secondary outcome results for study group	Secondary outcome results for the control group
Hajhashemi et al., (2019)	25-hydroxyvitamin D3 levels (ng/ml), before Tx 16.82±2.22, after 36.08±2.83, p-value <0.001	25-hydroxyvitamin D3 levels (ng/ml), before Tx 16.77±2.32, after 16.25±2.24, p-value 0.315
Arjeh et al., (2020)	Vitamin D level (ng/mL): baseline 10.98 ± 2.01, after Tx 30.59 ± 4.46 Parathyroid hormone level (ng/L), baseline 45.91 ± 10.41, vs. 43.68 ± 11.65 after Tx Calcium level (mg/dL), baseline 8.02 ± 1.01, vs. 7.92 ± 1.11 after Tx	Vitamin D level (ng/mL): from 11.01± 1.99, to 15.68 ± 5.45 Parathyroid hormone level (ng/L), baseline 44.91± 11.11 vs. 43.68 ± 11.65 Calcium level (mg/dL), baseline 8.34 ± 0.91, vs. 8.01 ± 1.43
Tabrizian et al., (2021)	Vitamin D level, (ng/mL) baseline (deficiency group): 12.2±3.8 vs. 32.7±10.2 after Tx	Vitamin D level, (ng/mL) baseline (insufficiency group) 24.8±2.8 vs. 37.6±10.0, after Tx
Xess, S., & Sahu, J. (2020)	Vitamin D level (ng/ml): before Tx 19.9±1.0 vs. after Tx., 30.7±10.5, p- value <0.001 "Progression to extensive disease" or a significant worsening of fibroids related symptoms: 5.0% got pregnant, 11.6% underwent medical or surgical Tx	Vitamin D level (ng/ml): baseline level 21.4±8.4 vs. After 23.1±7.6, p-value 0.38 "Progression to extensive disease" or a significant worsening of fibroids related symptoms: 8% got pregnant, 34% underwent medical or surgical
Miriello et al., (2021)	Myoma's vascularization: a decrease of the peripherical vascularization in the 7.7% of treated patients (36.3% pre-Tx vs. 28.6% after Tx) The number of myomas did not change Pelvic pain: visual analogue scale (VAS) scale median value was 4 before Tx and 2 after Tx (p-value: 0.03) Heavy menstrual bleeding: (56% of patients) vs (41%) p- value 0,09 Women's health and quality of life: a mean score pre-Tx of 61.86 vs. 80.77 post-Tx (p-value <0.001) (by Short Form Health Survey 36 (SF-36))	Myoma's vascularization: an increase of 5.5% (38.8% pre-Tx vs. 41.1% after Tx) The number of myomas did not change Pelvic pain: visual analogue scale (VAS) a value of 4 both at baseline and after Tx Heavy menstrual bleeding: (50% of patients) vs (48.1%) p-value 0.9 Women's health and quality of life: a mean score pre-Tx of 59.45 ± 8.98 vs. 67.41 ± 9.11 after Tx, p-value 0.21

Table 5: *Summary of secondary outcomes by groups.*

Porcaro G., & Angelozzi P., (2021)	Bleeding: normal bleeding was restored in 82% of patients Fatigue: only 13% of women reported fatigue Pelvic pain: only one patient experienced the symptom Anemia: (4.5% had anemia at the end of the study), MeanHb levels (from 11.06 ± 0.70 g/dL at baseline to 11.43 ± 0.48 g/dL at 4 months; $p < 0.05$) Blood pressure: No significant changes	Bleeding: remained unchanged Fatigue: 52% of patients Pelvic pain: all patients who reported pelvic pain at baseline continued to report it Anemia: Hb levels (from 11.06 ± 0.91 g/dL at baseline to 11.00 ± 0.83 g/dL at 4 months; $p <$ 0.0001) Blood pressure: No significant changes
Porcaro et al., (2020)	The number of myomas did not change Quality of life showed an increase (31, median value) using LiKert format Severity of symptoms showed reduction (-7, median value), by LiKert format Bleeding patterns, 33.3% had normal bleeding, 0% had heavy bleeding, and 66.7% had medium bleeding Fatigue, 20% of patients Pelvic pain, 6.7%	The number of myomas did not change Quality of life showed a slight decrease (-1, median value) using LiKert format Severity of symptoms showed no variation (0, median value), by LiKert format Bleeding patterns, 20% had normal bleeding, 40% had heavy bleeding, and 40% had medium bleeding Fatigue, 53.3% of patients Pelvic pain, 53.3%
Orive et al., (2023)	Serum levels of (25(OH)D): (23.37 ± 37.29 vs. 37.02 ± 6.35, $p = 0.001$) Serum calcium: no significant changes, Serum AST, ALT, bilirubin: no significant changes, Serum creatinine: no significant changes	Serum levels of (25(OH)D): not reported Serum calcium: not reported, Serum AST, ALT, bilirubin: not reported. Serum creatinine: not reported

Note: Values are presented as mean ± standard deviation

Abbreviations: (UF/UFs: Uterine fibroid/s, Tx: Treatment, 25(OH)D: 25-hydroxyvitamin D3, Hb: Hemoglobin, AST: Aspartate transaminase, ALT: Alanine transaminase).

Table 5: *(continued) Summary of secondary outcomes by groups.*

mean age of participants across the studies ranged from 31.26 to 45.0 years. Older patients tend to have lower estrogen levels, which could lead to smaller fibroids, potentially masking the effects of vitamin D supplementation. Furthermore, the geographical origin of the study populations may have impacted baseline vitamin D levels and the response to supplementation, as regions with higher solar exposure may have higher natural vitamin D levels.

Regarding secondary outcomes, several CCT studies reported improved pain, quality of life, and other fibroid-related symptoms with vitamin D supplementation. Miriello et al. (2021) observed reductions in pelvic pain ($p = 0.03$) and improvements in quality of life ($p < 0.001$). Porcaro et al. (2021, 2020) also documented positive effects on bleeding, fatigue, pelvic pain, and symptom severity. Notably, most studies showed increased serum levels of 25(OH)D in the intervention groups. The findings on the inconclusive nature of vitamin D supplementation for fibroid size reduction align with some previous reviews, such as Combs et al. (2023). This recent review also highlights the potential of vitamin D based on preclinical evidence suggesting its anti-proliferative and anti-fibrotic effects on fibroid cells. However, discrepancies exist regarding the impact on secondary outcomes across studies. These variations might be due to differences in study methodologies, dosage regimens, and baseline vitamin D levels, as Amoah et al. (2021) emphasized.

The mixed findings across studies highlight the critical need for a standardized core outcome set in future fibroid research, as emphasized by Tran et al. (2020). Establishing a standardized set of essential outcomes consistently measured across studies would significantly enhance the comparability and generalizability of the findings. This approach would enable researchers to build on existing knowledge and offer more conclusive insights into the effectiveness of vitamin D supplementation for uterine fibroids. This systematic review's strengths lie in its comprehensiveness. Including both randomized controlled trials (RCTs) and controlled clinical trials (CCTs) allowed it to capture a broader spectrum of research on vitamin D supplementation for uterine fibroids. This approach offers a more holistic view of the current evidence. This review's limitations include the included studies' inherent methodological challenges and the potential for single-author bias. Most of the included studies are controlled clinical trials (CCTs), which are vulnerable to a moderate risk of bias, especially regarding selection bias, missing data, and outcome measurement. These factors can impact the generalizability of their results.

Additionally, the studies exhibited heterogeneity, meaning they included diverse populations, employed varying interventions (dosage, duration), and utilized different outcome measures. Two studies included other supplements, making isolating vitamin D's specific impact on uterine fibroid size and related outcomes difficult. This heterogeneity makes directly comparing findings and drawing definitive conclusions challenging. Furthermore, some studies did not fully explore potential confounding factors, such as lifestyle habits or co-existing medical conditions, which could influence the observed associations between vitamin D and fibroids.

Conclusion

Vitamin D supplementation has shown potential benefits for uterine fibroids in some studies, particularly in reducing fibroid size and improving associated symptoms. However, the evidence remains inconclusive due to the limited number of high-quality studies and the inconsistent findings across different study designs.

The limitations of the current research highlight the need for more rigorous studies with standardized methodologies. Future research should focus on well-designed RCTs with standardized protocols, including consistent vitamin D dosages and predefined outcomes established through a COS. Implementing a COS would ensure consistent reporting across studies, allowing researchers to build upon existing knowledge and provide more definitive answers regarding the effectiveness of vitamin D supplementation for uterine fibroids. Additionally, future research should explore optimal dosage and treatment duration, investigate the impact on specific fibroid subtypes or symptoms, and consider potential confounding factors like lifestyle habits and co-existing medical conditions. By addressing these limitations and conducting more rigorous research, we can better understand the true potential of vitamin D supplementation for managing uterine fibroids.

Funding

This research received no external funding.

Conflicts of Interest

The authors declare no conflict of interest.

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