Mashhad University of Medical Sciences (MUMS)

Reviews in Clinical Medicine

Clinical Research Development Center Ghaem Hospital

Efficacy of Vitamin D in the Treatment of Uterine Fibroids: A Systematic Review and Meta-analysis

Morvarid Irani (MD)[1], Ali Saberi (MD)[2], Zahra shojaeian (MD)[3], Mohamad Ghorbani (MD)[4], Nahid Maleki (MD)[5*]

[1]*Ph.D. in Reproductive Health, Department of Midwifery, School of Nursing and Midwifery, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran.*
[2]*Student Research Committee, School of Nursing and Midwifery, Mashhad University of Medical Sciences, Mashhad, Iran.*
[3]*Ph.D. in Reproductive Health, Department of Midwifery, Quchan Branch, Islamic Azad University, Quchan, Iran.*
[4]*Department of Public Health, School of Health, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran.*
[5]*Ph.D. in Reproductive Health, Department of Midwifery, School of Nursing and Midwifery, Shahroud University of Medical Science, Shahroud, Iran.*

ARTICLE INFO

Article type
Original article

Article history
Received: 02 May 2024
Revised: 10 Jun 2024
Accepted: 29 Sep 2024

Keywords
25-OH-D3
Fibroids
Myomas, uterine fibroids
Meta-analysis
Systematic review
Vitamin D supplementation

ABSTRACT

Introduction: Uterine fibroids or Leiomyoma (UFs) are one of a common problem that affects the quality of life in women. Recently use of vitamin D for treating Leiomyoma has been considered.
This Systematic Review was performed with aim to evaluate the current evidence for the efficacy of vitamin D in treating uterine fibroids.
Methods: Relevant studies were identified from the following Electronic searching of Medline, PubMed, Scopus, Cochrane, Embase, Web of Science, SID, and Google Scholar up to Feb 2024. Inclusion criteria consist of Both English and Persian-published, clinical trials using vitamin D as medical for treatment of uterine fibroids. In the long run, four RCTs met the inclusion criteria. The quality of these trials was evaluated by two researchers who carried out the data extraction, using Oxford Center for Evidence-Based Medicine checklist. Statistical analysis was performed by Comprehensive Meta-analysis (CMA) Version 2. To assess the publication bias and heterogeneity, Egger's and Begg's tests and I2 were used, respectively. In addition, the Random effects model was employed to perform the meta-analysis.
Results: The heterogeneity in the studies was determined as 95.17% ($p<0.000$). There was publication bias among the studies included; the p-values of Egger's and Begg's tests were 0.05 and 0.05, respectively. The effects of Vit D on UFs were statistically significant [mean difference (MD)=2.88; 95% confidence interval (CI): (4.72-1.044); $p<0.002$].
Conclusion: Vitamin D for treating uterine fibroids can be an effective method, but more studies are needed to confirm these findings.

Please cite this paper as:
Irani M, Saberi A, Shojaeian Z, Ghorbani M, Maleki N. Efficacy of Vitamin D in the Treatment of Uterine Fibroids: A Systematic Review and Meta-analysis. Rev Clin Med. 2024;11(3): 21-28.

Introduction

Leiomyoma's Uterine also known as fibroids, myomas, and leiomyomata are the most common benign pelvic tumors that originate in the smooth muscles of the uterus and their prevalence varies from 4.5% to 68.6% (1). leiomyomas are often asymptomatic, and their symptomatic types according to their size and location usually appear as abdominal pain, abnormal menstrual bleeding, anemia, infertility, and recurrent miscarriages (2,3). Sex hormones strongly affect the size and growth rate of leiomyomas, Therefore, increasing estrogen and progesterone

Corresponding author: Nahid Maleki
Department of Midwifery, School of Nursing and Midwifery, Shahroud University of Medical Science, Shahroud, Iran
Email: malekimidwife@gmail.com
Tel: *09154409434*

levels during fertility age is associated with an increased risk of uterine leiomyomas and regress after menopause (4). Therapeutic options including medical therapy, surgical interventions, and uterine artery embolization depend on fertility preservation and the patient's preference (5). Therapeutic agents like gonadotropin hormone-releasing hormone (GnRH) analog, oral GnRH antagonist, and selective progesterone receptor modulators, (6,7). Due to substantial side effects of hypoestrogenism, e.g., hot flush, which reduces bone mineral density, some treatments have limited usage, and prolonged use of this method is not possible (8).

Surgery is also one of the treatment options for fibroids, which varies from myomectomy to hysterectomy (9). Leiomyomas are still the most common cause of hysterectomy in women (10), but this method is not appropriate for women whose surgery is not possible in fertility preservation. Therefore, understanding the etiology of fibroids and reviewing new treatment strategies can eliminate the defects of previous methods. Gene therapy, tyrosine kinase inhibitors, aromatase inhibitors, cyclin-dependent kinase (CDK) inhibitors, curcumin, and vitamin D are among the new treatment strategies for treating fibroids (11).

Vitamin D may reduce the risk of chronic illnesses and neoplasms (12), and so Various studies have confirmed that lower serum 25(OH)D levels were associated with several gynecological and obstetrical pathologies (13,14). Recent studies have identified abnormal concentrations of vitamin D as important players in the etiology of UFs(15). Vitamin D (1, 25 (OH) 2D3) has strong anti-estrogen and progesterone effects and can be an appropriate treatment for suppressing leiomyomas (16-17). Vitamin D deficiency in African American women is higher than in other women, because higher melanin concentrations result in decreased serum vitamin D levels, and leiomyomas in these women are higher than in white women, which shows the important role of vitamin D in the development of leiomyomas (18).

The high prevalence of hypovitaminosis D was detected in research in Iran (19,20). The present data are insufficient to detect the role of vitamin D as a medical therapy for the treatment of uterine fibroids and it is still obscure whether long-term supplementation of vitamin D could reduce the risk or prevent the growth of UFs. Therefore, in this review study, we tried to collect all the published scientific articles related to the effect of vitamin D on leiomyomas. We hope that healthcare providers will be able to take a step towards promoting women's health by using the results of this study.

Materials and Method

Databases and search terms: This systemic review and meta-analysis, was designed and reported using a checklist of items in accordance with the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)" statement (21). The systematic electronic search was done on the databases of the MEDLINE, PubMed, web of science, Embase, Scopus, the Cochrane Central Register Trials inception, Google Scholar as well as Persian databases such as SID, Iran Medex, and Magiran up to March 2021 to evaluate the efficacy of vitamin D in the treatment of PMS. No determined limitation was considered and the search keywords were vitamin D AND uterine fibroids OR leiomyoma or fibroma.

Inclusion and Exclusion criteria

To be included in the review, the chosen articles expected to meet the accompanying criteria: All of the in-Vivo studies, Reproductive age women diagnosed with leiomyoma, Randomized Controlled Trials (RCTs), Interventions consist of vitamin D, Comparisons could consist of a placebo or any other interventions. Outcome measures include, Primary outcomes: change in diameter and volume of the fibroid by ultrasound examinations and the following issues were considered for Secondary outcomes: Adverse events, amounts of calcium and parathyroid hormones. Four studies assessed the effect of vitamin D on uterine fibroids.

Selection process

Figure 1 shows the process of selection of articles for this systematic review. The process of the search and selection of RCTs is shown in Figure1.

Data extraction

The data extraction and the quality assessment of the included trials were carried out by two separate individuals according to a predefined checklist, consist of; first author, year of publication, design, sample size, duration of treatment, dosage and outcome values for both the intervention and the control groups with the mean and standard deviation of pre- and post-treatment or mean difference from the baseline.

Quality assessment

Two reviewers using Oxford Center for Evidence Based Medicine checklist (Table 1) independently rated the quality of RCTs (22). This tool has been designed in two sections to evaluate internal and external validity. in this review, Internal Validity comprising of six general inquiries regarding the

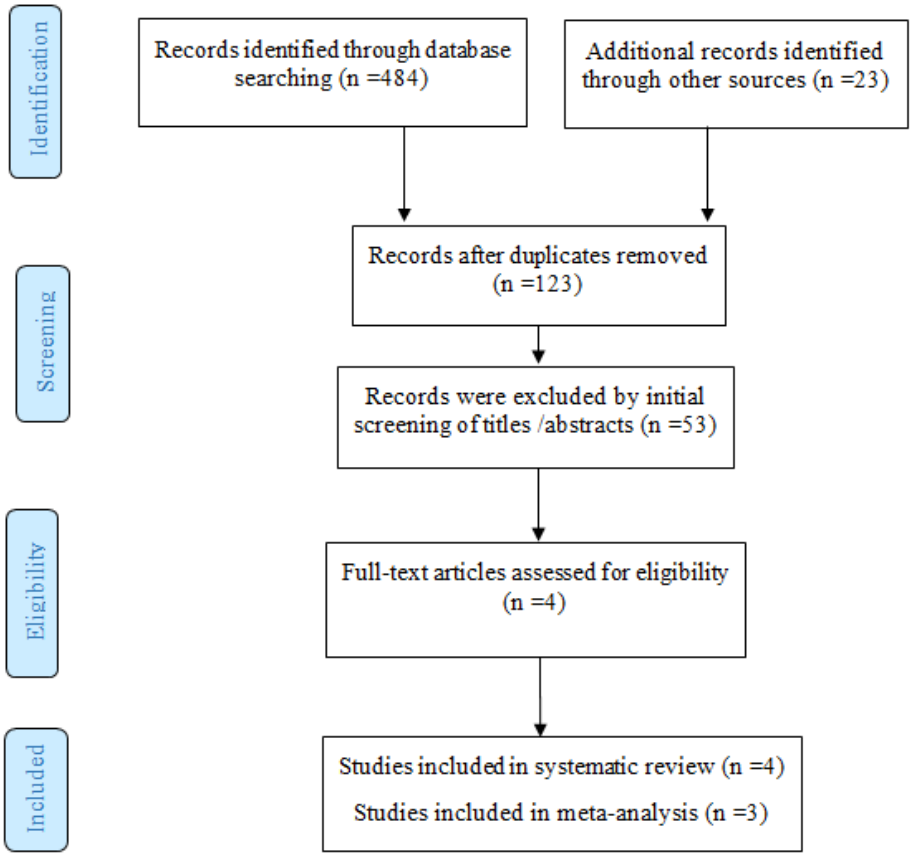

Figure 1. PRISMA Flow Diagram of study selection progress

method of patients' assignment, comparability and matching of groups, equality of allocated treatment, losses to follow-up and intention-to-treat analysis, blindness and effect size which was replied with three alternatives Yes / No and Unclear (23). Risks of bias assessment are shown in figure 2 and table 1.

Statistical Analysis

All statistical analyses were done by Comprehensive Meta-Analysis Version 2 (Bio stat, Englewood, NJ, USA).

Results

Of the 507 relevant publication trials, four CTs met the inclusion criteria. The summarized characteristics of the included studies (see Table 2). Out of the 4 studies, 2 studies were conducted in Iran, and the others in China, and Italy, Leiomyoma size was assessed by ultrasound in most studies (n=4). The language of 2 studies was English, and 2 studies were in Persian. The data extracted from the studies included in the review are presented in Table 2.

Arjeh et al. conducted a randomized double-

Table 1. Risk of bias summary: Systematic review. Author's judgments of risk of bias item for each included study

	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Did the analysis include an intention to treat analysis?
Arjeh et al. 2020	+	+	+	+	-	?	?
Ciavattini et al.2016	-	?	?	?	?	?	?
Domar et al. 2000	+	+	?	?	?	?	?
Gorayeb etal. 2012	+	+	+	+	-	+	?

blinded clinical trial to evaluate the safety of the vitamin D treatment for UFs during the 12-week study period. 60 women were randomly divided into two groups, the intervention group (n=27) received a weekly dosage of 50,000 IU oral vitamin D tablets and the control group received placebo (lactose sugar) tablets (n=28). The result showed that No statistically significant decrease in the volume of fibroids was observed in the experimental group [mean difference (MD): -0.71, 95% confidence interval (CI): - 0.1 to 1.53, P ¼ 0.085], and a significant increase was observed in the size of fibroids in the control group (MD: 2.53, 95% CI: 1.9 to 4.05, p = 0.001) (9).

Ciavattini et al. performed a cohort clinical trial, to evaluate the effect of vitamin D supplementation in women with UFs for 12 months. The intervention group (n=53) received 50,000 IU of cholecalciferol (oral solution) once per week for 8 weeks, followed by maintenance therapy of 2000 IU daily for a year, and the women with "small burden" UFs and hypovitaminosis D who did not properly perform the therapy or refused it, constituted the control group. In women with UFs, a negative correlation emerged between the baseline 25-hydroxy-cholecalciferol (25-OH-D3) concentration and both the volume of the largest fibroid (r=_0.18, P=0.01) and the total volume of fibroids (r=_0.19, P=0.01). No correlation was found between the baseline 25-OH-D3 levels and the number of fibroids per patient (r=_0.10, P=0.16). In women of the "study group," a significant increase in the 25-OH-D3 serum level was observed after 12 months of supplementation, and a lower rate of surgical or medical treatment due to the "progression to extensive disease" was reported (13.2% vs 30.9%, P=0.05). Supplementation therapy with 25-OH-D3 restores normal vitamin D serum levels in women with "small burden" fibroids. In these women, vitamin D supplementation seems to reduce the progression to an extensive disease, and thus the need for conventional surgical or medical therapy (10).

Hajhashemi et al. in a double-blind prospective clinical trial, investigated 69 patients with uterine leiomyomas aged 35 to 49 years (40.58±4.26) who met the inclusion criteria. They were randomized into two groups: the intervention group received vitamin D 50,000 IU every 2 weeks for 10 weeks and the other group received a placebo consisting of an exemplar without vitamin D3 with the same color and shape. According to t-test results, after a 10-week intervention, 25-hydroxyvitamin D3 levels were significantly higher in the group receiving vitamin D (36.08 vs 16.25 ng/ml). (P<0.001) Leiomyomas size in the VIT D group significantly decreased as compared to the placebo group (52.58 vs 61.11 mm, respectively) (24). Since the study of Sheng et al. (2020) was a protocol and despite the email and correspondence with the authors, no follows were received from their results (25).

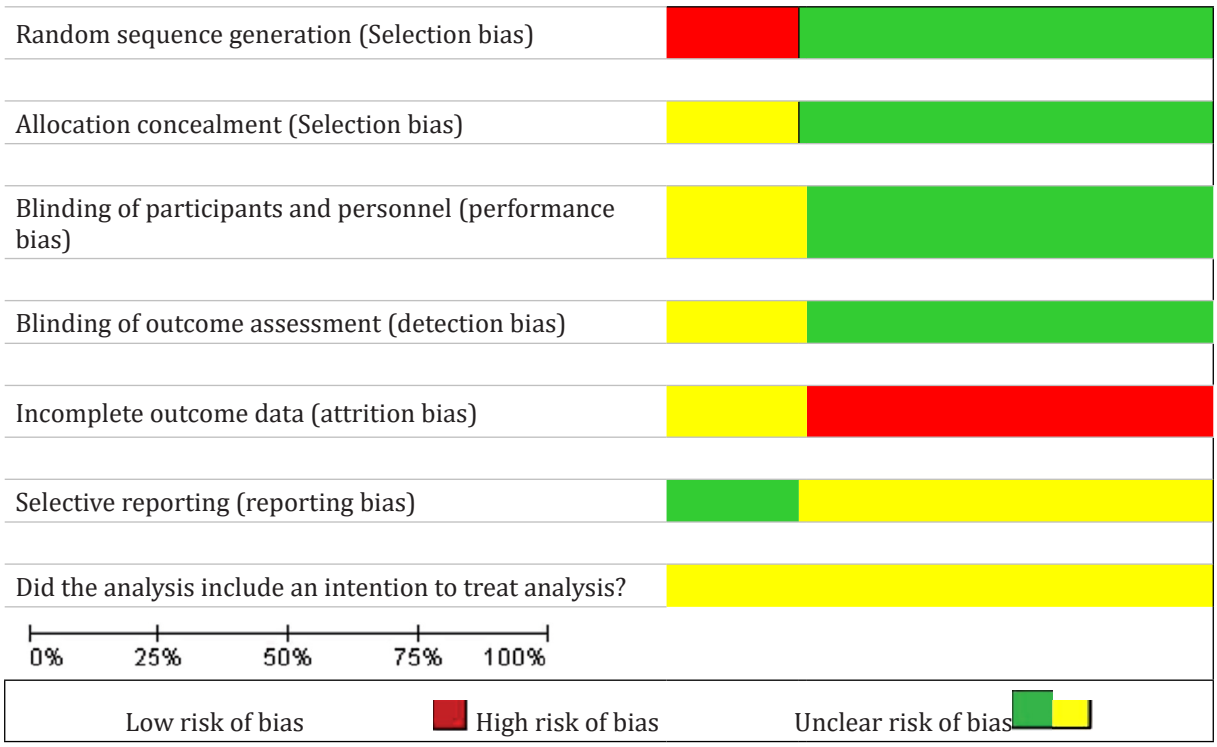

Figure 2. Risk of bias graph: Systematic review. Author's judgments of risk of bias presented as percentages across all included studies

Table 2. Characteristics of four trials included in systematic review

No	Author, Year	Design	Duration, (wk.)	Age (/Y)	Intervention mg	Type of control	Participants Intervention	Participants control	Baseline comparability	Dropouts (4)	Tools	blinding method	Adverse effects	Outcome(s)
1	Arjeh et al. (5), Iran	RCT	12	18–45	50,000 IU oral vitamin D tablets of saffron	placebo (lactose sugar) tablets	N= 30	N=30	Yes	8%	Laboratory tests and ultrasound evaluations	double-blind	There were no adverse effects.	No statistically significant decrease in the volume of fibroids was observed in the experimental group [mean difference (MD): -0.71, 95% confidence interval (CI): - 0.1 to 1.53, P =0.085], and a significant increase was observed in the size of fibroids in the control group (MD: 2.53, 95% CI: 1.9 to 4.05, p = 0.001).
2	Ciavattiniet al. (2016), I Italy	CT, cohort	12 months	Average 51	50,000 IU of cholecalciferol (oral solution) once per week for 8 weeks,followed by maintenance therapy of 2000 IU daily for a year	who did not properly perform the therapy or refused it	N=53	N=55	Yes	28%	Laboratory tests and ultrasound examination,	Not reported	No sign of vitamin D toxicity was reported	a negative correlation emerged between the baseline 25-hydroxy-cholecalciferol (25-OH-D3), concentration and both the volume of the largest fibroid (r=_0.18, P=0.01) and the total volume of fibroids (r=_0.19, P=0.01). No correlation was found between the baseline 25-OH-D3 levels and the number of fibroids per patient (r=_0.10, P=0.16). In women of the "study group," a significant increase in the 25-OH-D3 serum level was observed after 12 months of supplementation, and a lower rate of surgical or medical treatment due to the "progression to extensive disease" was reported (13.2% vs 30.9%, P=0.05).
3	Hajhashemi et al. (2019), Iran	RCT	10	35 to 49	vitamin D 50,000 IU every 2 weeks	placebo consisting of exepian without vit D3	N=35	N=35	Yes	1%	Laboratory tests and ultrasound	double-blind	No case of toxicity was observed.	25-hydroxyvitamin D3 levels were significantly higher in group receiving vitamin D (36.08 vs 16.25 ng/ml). (P<0.001) Leiomyomas size in vit D group significantly decreased as compared to placebo group (52.58 vs 61.11 mm, respectively).
4	Sheng et al. (5), China.	RCT	2 Y	35–50	oral dose of 1600 IU (four capsules)/day vitamin D3 for up to 2 years	Just follow-up at the same time points	N=180	N=180	Yes	Not reported	ultrasound examination,	single -blinded	Not reported	Not reported

Meta–analysis

Publication bias was assessed statistically using Egger's and Begg's tests. The p values of the Egger's and Begg's tests were 0.05 and 0.05, respectively, indicating that publication bias existed among the studies included. The unsymmetrical pattern of the funnel plot also confirmed the preceding statistical tests visually (Figure 3).

X-axis is the natural logarithm of the mean difference and the y-axis is the standard error of the natural logarithm of means.

The heterogeneity of the measure of effects

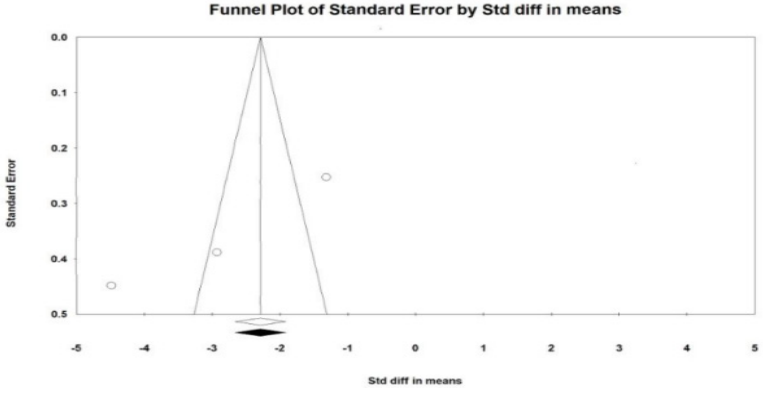

Figure 3. the funnel plot for the publication bias

among the studies was assessed based on I2, which was 95.17% (p<0.000). However, a Random effects model was applied to all calculations because there were some of the differences between the studies. All 3 studies were included in the meta-analysis, which resulted in a mean difference of 2.88 with 95% confidence interval (CI) (4.72-1.044), implying that the effects of Vit D on UFs were statistically significant (p<0.002). The forest plot, the mean difference, its CI, the corresponding weight of each individual study, the pooled mean difference, and its CI, are shown in Figure 4.

The horizontal lines denote the 95% CI, the Square (□) shows the point estimate (the size of the square corresponds to its weight); the diamond shows (◇) the combined overall effects of treatments.

OR: Odds ratio, CI: Confidence interval

Discussion

the present meta-analysis and review study support that vitamin D has positive effects in reducing the size or stopping the growth of fibroids, but it seems that due to the small number of RCTs performed on human models and small sample size, more studies are needed to clarify the issue as much as possible to achieve a definite and practical result. The results of a systematic review showed vitamin D supplementation significantly reduces the size of Ufs(26), of course, In this study, research conducted in Iran was not included. Kozłowsk et al (2023) conducted a review of the state of knowledge based on available studies and found Vitamin D promising, effective, and low-cost methods in the management of UFs and their clinical symptoms (27).

Perhaps in the last decades, the only positive feature of vitamin D found in the research was the protection of bone and calcium homeostasis, but today, as research progresses, vitamin D plays a protective role against many diseases such as cardiovascular disease, colorectal and breast cancer (and possibly other cancers), infections, auto immune disease, and adverse pregnancy outcomes, (17, 24, 28), improve menstrual disturbances and metabolic factors in polycystic ovary syndrome (PCOS) (29).

Halder et al. (2012) Conducted a study on Eker mice and found that vitamin D significantly decreased the size of fibroids by suppressing genes involved in cell growth and proliferation, estrogen and progesterone receptors, and anti-apoptotic genes (30). In addition, vitamin D through the down-regulation of proliferating cell nuclear antigen, cyclin-dependent kinase 1, and B-cell lymphoma 2 suppresses the expression and activity of catechol O-methyl transferase and inhibits the growth of fibroid cells (31). Research has shown that this is due to over-expression of collagen type 1 and fibronectin in uterine fibroids, treating with vitamin D, however, western blot analysis demonstrated a decrease in fibronectin and collagen type 1 expression in uterine fibroids, indicating yet another mechanism by which vitamin D might serve to inhibit uterine fibroid growth (32). Data from some studies suggested that vitamin D may be inversely related to the growth of UFs (33). Davari Tanha (2021) reported that 50000 IU vitD for 8-week administration among vitD insufficient women, can inhibit leiomyoma growth (34). Miriello (2021) reported the effectiveness and safety of combined supplementation of vitamin D + epigallocatechin gallate (EGCG) + vitamin B6 for 4 months of administration among women with UFs in reducing myomas' size and improving patients' quality of life (35). Ciavattini (2016) showed that prescribing vitamin D supplementation in women with uterine fibroids and concomitant hypovitaminosis D leads to reduced progression to an extensive disease (36).

Ciebiera (2018) suggested that further studies about the biological effect of vitamin D on UFs biology are required. Vitamin D preparations (alone or as co-drugs) could become new tools in combat with UFs, with the extra beneficial pleiotropic effect (15).

The limitations of the current study are few studies focused on appropriate inclusion criteria.

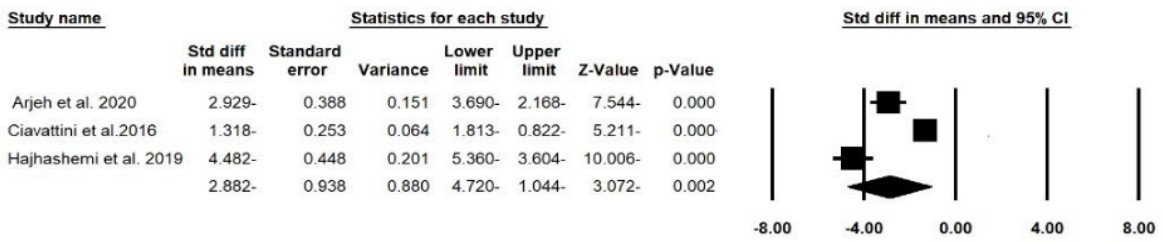

Figure 4. The effects of VIT D on UFs based on the mean difference

On the other hand, the dosage of vitamin D supplementation and patients' baseline serum vitamin D levels varied from study to study that may affect the advantage of the treatment, also publication bias could be a threat to the validity of the results, and so the findings should be interpreted with cautiousness.

Conclusion

The main finding of this study which is vitamin D for treating UFs can be an effective method, but more studies are needed to confirm these findings. Many hysterectomies are performed each year in the world fibroids being the most common indication for this procedure, while surgical treatment for UFs is the associated risks of morbidity, mortality, and infertility cannot be overlooked and the need for a safe effective nonsurgical therapeutic strategy is critical. According to the mentioned mechanisms of the effectiveness of vitamin D on uterine fibroids, if more studies are performed and determine the exact dosage and details of effective use, healthcare providers can take steps to improve the health of females with uterine fibroids. Author Contributions: conceptualization and experiments design: M.I and N.M. data handling and Draft Manuscript: M.I, N.M, A.S, and M.GH. Data analysis: M.I and N.M. draft preparation: M.I A.S and N.M. writing and reviewing, and project administration: M.I, N.M, and M.GH. Analysis and interpretation of data; M.I, N.M, A.S, Z.SH, and M.GH. Study validation, supervision; All authors.

Conflict of interest

No potential conflicts of interest were disclosed.

Acknowledgments

The authors extend their deepest thanks to all the researchers who provided them with additional information on their studies.

References

1. Marsh EE, Al-Hendy A, Kappus D, et al. Burden, Prevalence, and Treatment of Uterine Fibroids: A Survey of U.S. Women. J Womens Health (Larchmt). 2018; 27:1359-1367.
2. Al-Hendy A, Salama S. Gene therapy and uterine leiomyoma: a review. Hum. Reprod. Update. 2006; 12:385-400.
3. Ali M, Al-Hendy A, Yang Q. Vit D, a promising natural compound with anti-uterine fibroid characteristics. Fertil Steril. 2019; 111: 268-269.
4. Al-Hendy A, Lee EJ, Wang HQ, et al. Gene therapy of uterine leiomyomas: adenovirus-mediated expression of dominant negative estrogen receptor inhibits tumor growth in nude mice. AJOG. 2004; 191:1621-31.
5. Parker WH. Etiology, symptomatology and diagnosis of uterine myomas. Fertil Steril 2007; 87: 725-36.
6. Nair R, Maseeh A. Vitamin D: the "sunshine" vitamin. J Pharmacol Pharmacother. 2012; 3: 118-126.
7. Bikle, D.D. Vitamin D and immune function: Understanding common pathways. Curr Osteoporos Rep. 2009; 7: 58–63.
8. Muhammad, J., Yusof, Y., Ahmad, I. et al. Elagolix treatment in women with heavy menstrual bleeding associated with uterine fibroid: a systematic review and meta-analysis. BMC Women's Health. 2022; 22: 14-22.
9. Arjeh S, Darsareh F, Asl ZA, et al. Effect of oral consumption of vitamin D on uterine fibroids: a randomized clinical trial. Complement Ther Clin Pract. 2020; 39:101159.
10. Ciavattini A, Carpini GD, Serri M, et al. Hypovitaminosis D and "small burden" uterine fibroids: Opportunity for a vitamin D supplementation. Medicine. 2016; 95:52-58.
11. Taylor DK, Leppert PC. Treatment for Uterine Fibroids: Searching for Effective Drug Therapies. Drug Discov Today Ther Strateg. 2012; 9: 41-49.
12. Holick, M.F. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. Rev Endocr Metab Disord. 2017; 18: 153–165.
13. Skowronska, P, Pastuszek, E, Kuczynski, W, et al. The role of vitamin D in reproductive dysfunction in women—A systematic review. Ann. Agric. Environ. Med. 2016; 23: 671–676.
14. Whynott, R.M., Vaught, K.C.C, Segars, J.H. The effect of uterine fibroids on infertility: A systematic review. Semin. Reprod. Med. 2017; 35: 523–532.
15. Ciebiera, M., Włodarczyk, M., Ciebiera, M., et al. Vitamin D and uterine broids—review of the literature and novel concepts. Int. J. Mol. Sci. 2018; 19: 20-51.
16. Al-Hendy A, Diamond MP, El-Sohemy A, et al. 1, 25-dihydroxyvitamin D3 regulates expression of sex steroid receptors in human uterine fibroid cells. J Clin Endocrinol Metab. 2015; 100: 572-82.
17. Irani M, Mirzaei K, Maleki N, et al. The role of vitamin D in male and female reproductive health: a review study. IJOGI. 2017; 20:98-109.
18. Sabry M, Halder S, Ait Allah A, et al. Serum vitamin D3 level inversely correlates with uterine fibroid volume in different ethnic groups: a cross-sectional observational study. Int J Womens Health. 2013; 5:93-100.
19. Hashemipour, S., Larijani, B., Adibi, H. et al. Vitamin D deficiency and causative factors in the population of Tehran. BMC Public Health 2004; 4:38.
20. Hosseinpanah, F., Rambod, M., Hossein-nejad, A. et al. Association between vitamin D and bone mineral density in Iranian postmenopausal women. J Bone Miner Metab. 2008, 26; 86–92.
21. David Moher, Alessandro Liberati, Jennifer Tetzlaff, et al; the PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Ann Intern Med.2009; 151:264-269.
22. Jadad AR, Moore RA, Carroll D, et al. assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled clinical trials. 1996; 17:1-12.
23. Samad F, Saeed Z, Hasan Z, et al. Evidence Based Medicine. TPMJ. 2018; 25:896-902.
24. Hajhashemi M, Ansari M, Haghollahi F, et al. The effect of vitamin D supplementation on the size of uterine leiomyoma in women with vitamin D deficiency. CJIM. 2019; 10:2.
25. Sheng B, Song Y, Liu Y, et al. Association between vitamin D and uterine fibroids: a study protocol of an open-label, randomized controlled trial. BMJ Open. 2020; 6: 10-11.
26. Alsharif, S. A., et al. Eect of Oral Consumption of Vitamin D on Uterine Fibroids: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. Nutrition and Cancer. 2024; 76: 226-235.
27. Kozłowska M, Woźniak A, Sydor P, et al. Efficacy and potential use of vitamin D in the prevention and treatment of uterine fibroids. Journal of Education,

Health and Sport. 2023; 45: 107-121.
28. https://tbinternet.ohchr.org/Treaties/CRC/Shared%20Documents/SWE/INT_CRC_NGO_SWE_19075_E.pdf.2020 hwwidgdii-dGi-e-b-f-t-f-s-m-o-l.
29. Shojaeian Z, Sadeghi R, Latifnejad Roudsari R. Calcium and vitamin D supplementation effects on metabolic factors, menstrual cycles and follicular responses in women with polycystic ovary syndrome: A systematic review and meta-analysis. Caspian J Intern Med 2019; 10: 359-369.
30. Halder SK, Sharan C, Al-Hendy A. 1, 25-dihydroxyvitamin D3 treatment shrinks uterine leiomyoma tumors in the Eker rat model. Biology of reproduction. 2012; 86:1-10.
31. Sharan C, Halder SK, Thota C, et al. Vitamin D inhibits proliferation of human uterine leiomyoma cells via catechol-O-methyltransferase. Fertility and sterility. 2011; 95:247-53.
32. Halder Sk, Goodwin JS, Al-Hendy A.1, 25-Dihydroxyvitamin D3 reduces TGFbeta-3-induced fibrosis-related gene expression in human uterine leiomyoma cells. J Clin Endocrinol Metab. 2011; 96:754-762.
33. Mohammadi, R., Tabrizi, R., Hessami, K. et al. Correlation of low serum Vitamin-D with uterine leiomyoma: a systematic review and meta-analysis. Reprod Biol Endocrinal. 2020; 18: 85.
34. Davari Tanha F, Feizabad E, Vasheghani Farahani M, et al. The effect of vitamin D deficiency on overgrowth of uterine fibroids: a blinded randomized clinical trial. Int J Fertil Steril. 2021; 15: 95-100.
35. Miriello D, Galanti F, Cignini P, et al. Uterine fibroids treatment: do we have new valid alternative? Experiencing the combination of vitamin D plus epigallocatechin gallate in childbearing age affected women. Eur Rev Med Pharmacol Sci. 2021; 25:2843-2851.
36. Ciavattini A, Carpini GD, Serri M, et al. Hypovitaminosis D and “small burden” uterine fibroids: Opportunity for a vitamin D supplementation. Medicine. 2016;95:52-56.