



Original article

**Possible Impacts of Vitamin-D Supplements on Uterine Fibroid**

Ahmed A. Taha <sup>1</sup>, Fatma Amer Elsayed <sup>1</sup>, Reham S. Al-Fakharany <sup>2</sup> & Yasser Khamis <sup>1</sup>

<sup>1</sup> *Obstetrics and Gynecology Department, Faculty of Medicine, Beni-Suef University*

<sup>2</sup> *Department of Medical Physiology, faculty of Medicine, Beni-Suef University*

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**Abstract**

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**Corresponding Author:**

Fatma Amer Elsayed

[mrifai01119189570@gmail.com](mailto:mrifai01119189570@gmail.com)

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**Background:** Uterine fibroids, which are non-cancerous tumors found in the pelvic region, are prevalent among women of reproductive age. The incidence of uterine fibroids varies between 5.4% and 77%. These tumors develop within the muscular walls of the uterus in women who have not yet reached menopause. Symptomless or causing abnormal bleeding, pelvic pressure symptoms, infertility, and growth or regress throughout life, leiomyomas are more common in people of African descent, those who have never given birth, those who are overweight, and those with a positive family history of fibroids. Millions of women suffer with leiomyoma, and it is one of the most common reasons for hysterectomy. **Aim of the Work:** to determine whether or not vitamin D supplementation reduces the size of uterine fibroids in patients who are deficient in the nutrient. **Patients and Methods:** This RCT was a single-blind randomized study at tertiary care hospital at Beni-Suef university hospital from January 2022 till June 2022 and performed on a total of 100 women in childbearing period diagnosed with uterine fibroid who had vitamin- D deficiency. **Results:** As regards the fibroid size after Vitamin D

supplementation for 6 months, according to the findings of this study, there is no statistically significant distinction in fibroid size amongst Vitamin D group and control group over the first three months whereas, fibroid size was substantially less in the Vitamin D group. At the fourth, fifth month and sixth months. Consequently, the size of the tumor decreased significantly over the six months in the group of Vitamin D supplementation with no significant improvement in the size of the fibroid over the 6 months in the control group. **Conclusion:** According to the results of the current research, vitamin D supplementation is an effective, low-risk method of preventing leiomyoma growth and stabilizing fibroids, therefore avoiding the onset of more serious and symptomatic disorders. Vitamin D supplementation seems to prevent fibroid growth.

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## **1. Introduction**

Depending on the patient's age, the purpose for treatment, the patient's concern for fertility preservation, and the patient's preference, a variety of treatments, including medication, surgery, and embolization or ablation of the uterine artery, may be recommended [1].

Some women prefer to preserve their uterus and fertility rather than undergo the more common surgical methods of treating symptomatic fibroids (hysterectomy or myomectomy). Therefore, it appears that the potential downside of less risky treatments and intervention needs to be taken into account. Some research has focused on the connection between poor nutrition and the development of leiomyoma. High fruit consumption may minimize the risk of leiomyoma in black

women, while consumption of dairy products, omega-3 fatty acids, soybean milk, food additives, and sweets all raise the risk [2].

**Vitamin-D** (also referred to as “calciferol”): is a fat-soluble vitamin that is naturally present in a few foods, added to others, and available as a dietary supplement. It is also produced endogenously when ultraviolet rays from sunlight strike the skin and trigger vitamin- D synthesis. 1,25-dihydroxyvitamin D, often known as calcitriol, is the active form of vitamin D” [3].

Vitamin D has garnered significant attention in recent times due to its potential anti-carcinogenic properties, with particular attention given to colorectal cancer, breast cancer and skin cancers. for colorectal cancer: vitamin D can be an economical and secure way of reducing the

incidence and improving prognosis in colorectal cancer, doses of vitamin D3 between 1,000 and 2,000 IU per day could reduce the incidence of colorectal cancer, as In order to ensure that the serum level remains above 33 ng/mL, it was observed that there is a 50% reduced risk of colorectal cancer when the serum 25(OH)D level is equal to or greater than 33 ng/mL, as compared to when it is equal to or less than 12 ng/mL[4].

For breast cancer: vitamin-D affects the cell cycle, apoptosis, hormone receptors, angiogenesis, and hypoxia, all of which are related to breast cancer growth, progression and metastasis, Further studies have found that There has been a decrease in the occurrence of breast cancer of forty-five percent from the highest to the lowest quintile of circulating plasma levels of active 25 hydroxy-vitamin D3 in 25 studies [5].

For skin cancers: It is recommended that increased exposure to sunlight is overall beneficial and that Elevated amounts of vitamin D may potentially enhance the prognosis of melanomas [6].

As a result, the assumption was plausible, this could have a function in the pathophysiology of uterine fibroids. Although calcidiol serum levels were found to be insufficient in fibroid-afflicted females, administration of the medicine resulted in smaller tumors. It just took 0.5 g/kg/d to get these outcomes. MMP-2 and MMP-9 appeared to be two of the enzymes affected. and it decreases catechol-o methyltransferase (COMT), MMPs affect

many stages of tumor development, facilitating its growth through encouraging tumor growth, invasion, migration, angiogenesis, and suppression of apoptosis, it is possible to sustain tumor growth [7].

This research supports the initiation of clinical trials to determine whether vitamin-D may be used as a long-term medicinal therapy for the treatment of fibroids [7].

## **2. Patients and Methods**

This research was a randomized controlled trial (RCT) conducted in a tertiary care setting at a Beni-Suef University-affiliated hospital. Between the months of January 2022 and June 2022, the research was done and carried on a total of 100 women in childbearing period diagnosed with uterine fibroid who had vitamin- D deficiency.

### **Sample size:**

The determination of the sample size was conducted utilizing G power C software version 3.1.7, which was produced by the Institute of Experimental Psychology at Heinrich Heine University in Dusseldorf, Germany. Based on the effect size of 0.68 from prior studies, the minimum number of patients needed in each group was (50). Type 1 error of 0.05, two-tailed (two-tail) power of 90% (9).

### **Inclusion criteria:**

- 1) Patients having one or more uterine fibroids diagnosed by ultrasound, and complaining

from pelvic pain, heavy menstrual bleeding, intermenstrual bleeding, pressure symptoms, and or swellings.

- 2) Age group; (20-45) years
  - a. Serum level of vitamin- D3 less than (20ng/ml)
  - b. Overweight patients with BMI more than 25 and less than 30.

**Exclusion criteria:**

- 1) Patients with vitamin-D3 level more than 20ng/ml
- 2) Age less than 20 or more than 45 years.
- 3) Patients with submucous uterine fibroids.
- 4) Evaluation of the uterus using sonography is challenging, if adenomyosis is present.
- 5) Severe vaginal bleeding.
- 6) Patients reporting malignancy, Diabetes Mellitus, Multiple Sclerosis, autoimmune disorders and coronary, hepatic, or renal diseases.
- 7) Pregnancy, planning of pregnancy in near future, menopause, hormonal treatment (including oral contraceptive) during the past 3 months.
- 8) Supplemental vitamin D and long-term drug use.
- 9) Lack of interest in continuing research participation, poor vitamin D use, and loss of follow-up as a result of numerous causes.

10) Infertility, fibroid degeneration, or other indications for surgery.

11) History of previous myomectomy, history of total thyroidectomy, abortion or and pregnancy loss in past 6 months.

12) Medications affecting Vitamin-D metabolism such as (phenytoin, Carbamazepine, Epirubicin, Taxol, Tamoxifen, Clotrimazole, Rifampicin, Dexamethasone, Nifedipine, Spironolactone, Efavirenz, Ritonavir, Saquinavir, Cyproterone acetate).

- Celiac disease, chronic renal illness, and liver disease are just a few examples of conditions that interfere with vitamin D metabolism.

**Methodology**

100 Patients with uterine fibroids and vitamin-D deficiency were enrolled in single blinded randomized controlled study (block randomization) in which patients were divided into 10 blocks of size 10, each block was randomized such that 5 patients are allocated to group A and 5 to group B.

Patients are overweight with BMI more than 25 and less than 30

$$\text{BMI} = \text{weight per kg} \div (\text{height per m}) \times 2$$

**Group A:** 50 patients received 50, 000 IU of vitamin- D3(ossofortin 50, 000IU) every week till reaching level of (30 ng/ml), then a maintenance dose of 2000 IU is given daily.

**Group B:** 50 patients receiving regular treatment of uterine fibroid.

Then the size of fibroid was measured by abdominal ultrasound every month in both groups after treatment.

Also, vitamin-D level was measured every month.

**Outcome:**

Patients with vitamin D insufficiency saw a reduction in uterine fibroid size following 6 months of vitamin D administration.

**Statistical Analysis:**

The data was collected and entered to an Excel sheet. The statistical analysis was carried out using SPSS (SPSS Inc., Chicago, Illinois, USA). Numerical variables were expressed using mean and standard deviation and categorical data were expressed using number and percentage. The level of significance between different exposed groups was based on the analysis of variance test (independent t-test) for normally distributed data. For paired groups, paired t-Test was used. For categorical data, chi-square test was used. P values  $\leq 0.05$  were regarded to indicate a statistically significant difference between means.

**Ethical considerations:** the study protocol was approved by the research ethics committee of faculty of medicine of Beni-Suef University no. FMBSUREC/05122021/Elsayed.

**3. Results:**

This is a single blinded randomized controlled trial during which 100 females with uterine fibroid enrolled in the study. The group has been divided into 2 subgroups, group 1 included 50 females who receive Vit D supplementation while group 2, the control group, receive symptomatic treatment. Both groups were matched at the start of the analysis. In terms of demographics, the two groups did not differ significantly from one another (age, BMI, parity, age at menarche, sun exposure) and clinical characteristics (Vit D level at the beginning of the study and size of the fibroid) (Table 1). Most of the studied patients were less than or equal to 35 years old. The majority were overweight and parity 2 or more (Table 2). The group who receives Vit D supplementation showed sufficient level of Vit D while all studied patients in the control group showed Vit D deficiency (Table 3). Both the mean and the mean difference of vitamin D levels at 6 months were significantly different between the vitamin D group and the control group (Table 4). There is no significant difference in the size of the fibroid between Vit. D group and control group over the first three months while at the fourth visit, the Vit. D group had much smaller fibroids, fifth month and sixth months (Table 5). In every month, the Vit. D Group had a smaller mean difference than the other groups. All females show improvement in the level of Vit D after 6 months regardless of their age, or

parity (Table 6). The size of the tumor decreased significantly over the six months in the group of Vit D supplementation there is almost no change in the size of fibroid over the

6 months **and** In the control group, fibroid size did not significantly decrease during the course of the study's 6-month follow-up (Table 7).

**Descriptive analysis**

**Table (1):** Characteristics at baseline of the female participants investigated

	Group				P-value
	Vitamin D		Control		
	Mean	SD	Mean	SD	
<b>Age</b>	33	6	32	5	0.352
<b>Parity</b>	3	1	3	1	0.375
<b>BMI</b>	26.6	2.5	27	3.0	0.274
<b>Sun</b>	55	32	48	37	0.341
<b>Vit D M0</b>	11.7	3.6	11.1	3.7	0.417
<b>Size M0</b>	73	11	74	11	0.878

This table shows that both groups were matched at the start of the analysis. In terms of demographics, neither group differed significantly from the other (age, , parity, BMI, age at menarche, sun exposure) and clinical characteristics (Vit D level at the beginning of the study and size of the fibroid).

**Table (2):** Vitamin D levels in the control and vitamin D groups six months after intervention.

	Group				p-value
	Vitamin D		Control		
	Mean	SD	Mean	SD	
<b>Vit D M6</b>	38.9	3.9	11.2	3.7	0.001
<b>Vit D 6 (difference)</b>	27.2	1.0	.0	.2	0.001

This table showed that Six months into the study, statistically speaking, a difference could be seen between the vitamin D group and the control group in terms of both the mean and the mean difference of vitamin D levels.

**Table (4):** Comparison of fibroid growth in the control and vitamin D groups 6 months after intervention.

Size/mm	Group				p-value
	Vitamin D		Control		
	Mean	SD	Mean	SD	
Size M1	72	11	74	11	0.570
Size M2	72	11	74	11	0.540
Size M3	71	12	74	11	0.450
Size M4	69	12	74	11	0.048*
Size M5	68	11	74	11	0.016*
Size M6	67	11	74	11	0.006*

*\*P-value is significant*

This table showed that over the course of the first three months, there was no statistically significant difference in fibroid size between the Vit. D group and the control group while Four, five, and six month fibroid size was considerably less in the vitamin D group. Also, The Vitamin D Group had a consistently reduced mean difference throughout all months.

**Table (5):** Mean size of the fibroid over the 6 months in the VIT D group (Group 50)

		Mean	Std. Deviation	P-value
Pair 1	Size M0	73.18	11.435	0.001*
	Size M1	72.30	11.445	
Pair 2	Size M1	72.30	11.445	0.013*
	Size M2	72.18	11.435	
Pair 3	Size M2	72.18	11.435	0.001*
	Size M3	71.14	11.503	
Pair 4	Size M3	71.14	11.503	0.001*
	Size M4	69.10	11.601	
Pair 5	Size M4	69.10	11.601	0.001*
	Size M5	68.18	11.423	
Pair 6	Size M5	68.18	11.423	0.001*
	Size M6	67.30	11.479	

*\*P-value is significant*

This table shows that there is a change in the size of fibroid over the 6 months in the vitamin D group.

**Table (6):** Mean size of the fibroid over the 6 months in the control group (Group 50)

		Mean	Std. Deviation	P-value
Pair 1	Size M0	73.52	10.681	0.322
	Size M1	73.54	10.691	
Pair 2	Size M1	73.54 <sup>a</sup>	10.691	-----
	Size M2	73.54 <sup>a</sup>	10.691	
Pair 3	Size M2	73.54 <sup>a</sup>	10.691	-----
	Size M3	73.54 <sup>a</sup>	10.691	
Pair 4	Size M3	73.54	10.691	0.159
	Size M4	73.58	10.712	
Pair 5	Size M4	73.58	10.712	0.322
	Size M5	73.60	10.725	
Pair 6	Size M5	73.60 <sup>a</sup>	10.725	-----
	Size M6	73.60 <sup>a</sup>	10.725	

a. The correlation and t cannot be computed because the standard error of the difference is 0.

This table shows that there was no significant improvement in the size of the fibroid over the 6 months.

#### 4. Discussion:

Uterine fibroids (UFs) are a type of smooth muscle cell tumor that affects women at an alarming rate. The incidence of leiomyomas among reproductive-aged women varies widely, from 5.4% to 77%, depending on the diagnostic procedure used and the population studied in various epidemiological studies [8].

Vitamin D is a crucial component of human nutrition. Vitamin D has recently been investigated for its potential role in UF formation [9].

Angiogenesis, extracellular matrix synthesis, and immunological response are just few of the biological processes that are affected by vitamin D's functional effects, which also include inhibited cell proliferation and increased apoptosis and enhanced differentiation. It has

been proposed that a positive feedback loop between extracellular matrix formation and cell proliferation is involved in the pathophysiology of fibroids, and that vitamin D may help to prevent this loop [10].

Consequently, this study was conducted recruited patients with vitamin D insufficiency and set out to assess the impact of vitamin D supplementation on the growth of uterine fibroids.

This research was a randomized controlled experiment with one-way blinding conducted at a Beni-Suef University-affiliated tertiary care center. The study was conducted over a period of six months, from January 2022 to June 2022 and performed on a total of 100



women in childbearing period diagnosed with uterine fibroid who had vitamin- D deficiency.

All told, 122 potential trial participants were screened, and 100 (50 in each group) were ultimately included. Fourteen patients met eligibility but were not included in the trial because they did not meet one of the inclusion criteria, and eight patients declined to participate.

The analysis relied on the data provided by 100 women in child bearing period diagnosed with uterine fibroid who had vitamin- D deficiency separated into halves: **Group (A)** which included 50 females who received Vit D supplementation. **Group (B)**, the control group which included 50 females who received symptomatic treatment.

The current investigation found no appreciable variations in either set of demographics. (age, BMI, parity, age at menarche, sun exposure) (p values = 0.352, 0.274, 0.375, 0.120) respectively and clinical characteristics (Vit D level at the beginning of the study and size of the fibroid) (p values = 0.417, 0.878) respectively.

After Vitamin D supplementation for 6 months, the current study results revealed that the group who receive Vit D supplementation showed a sufficient level of Vit D while all studied patients in the control group showed Vit D deficiency with a large disparity between mean and average vitamin D levels at 6 months between the Vit. D group and control group (p value=0.001).

As regards the fibroid size after Vitamin D supplementation for 6 monthsIn the present study, the researchers found that the Vit. D group and the control group did not differ significantly in fibroid size throughout the first three months while the size of the fibroid was significantly lower in the Vit. D group at the fourth, fifth month and sixth months.

Consequently, the size of the tumor decreased significantly over the six months in the group of Vit D supplementation (p value>0.001) with no significant improvement in the size of the fibroid over the 6 months in the control group.

Recent studies have shown that vitamin D can inhibit the proliferation of uterine fibroid cells, suggesting it may have anticancer effects and reducing the size of fibroid lesions. [2, 12, 13, 14]. Recent research has found that Vitamin D deficiency increases a woman's risk of developing uterine fibroids. Vitamin D administration reduces uterine fibroid cell proliferation, according to research by **Al-Hendy and Badr [15]**. Women who had enough vitamin D were found to have a lower risk of UFs by **Baird et al. [16]**.

Consistent with prior research, our results are. The efficacy of vitamin D supplementation in women with hypovitaminosis D and uterine fibroids was studied by **Ciavattini et al. [17]** in prospective research that included 108 women with uterine fibroids and concurrent hypovitaminosis D indicated the presence of a negative association between the initial concentration of 25-hydroxy-cholecalciferol

(25-OH-D3) and both the volume of the largest fibroid ( $r = -0.18$ ,  $P = 0.01$ ) as well as the overall volume of fibroids ( $r = -0.19$ ,  $P = 0.01$ ). After 12 months of supplementation, the 25-hydroxyvitamin D3 (25-OH-D3) serum level significantly increased among the women in the "study group," and it was stated that the rate of surgical or medicinal therapy due to "progression to extensive disease" was reduced (13.2% vs 30.9%,  $P=0.05$ ).

Consequently, it appears that vitamin D supplementation slows the spread of disease, reducing the need for invasive medical procedures [17]

In agreement with our results, Vahdat et al. (2011) conducted a randomized, double-blind, placebo-controlled research with a cohort of 109 women who had previously undergone hysteroscopic myomectomy and were found to have vitamin D insufficiency whose participants were given either a daily 1000 IU pill of vitamin D ( $n = 55$ ) or a placebo ( $n = 54$ ) for a period of 12 months in order to examine the impact of vitamin D supplementation on the recurrence of uterine fibroids. The average age of the participants was  $37.9 \pm 6.5$  years. In terms of demographics and health prior to the intervention, there were no notable differences between the two groups. Supplementation with vitamin D for a year cut UF recurrence rates in half. Recurrent UF was smaller in the vitamin D intervention group than in the control group (7.7 mm), a statistically significant difference ( $p < 0.001$ )

Researchers Halder et al. [18] discovered in 2012 that inhibiting cell growth and proliferation-related genes, antiapoptotic genes, and estrogen and progesterone receptors with 1,25-OH-D3 dramatically reduced fibroid tumor size in Eker rats. These findings have important clinical implications since vitamin D may offer a safe, non-invasive treatment option for uterine fibroids.

**Paffoni et al. [19]** undertook a case-control study with 128 breast cancer patients and healthy controls.

Similar findings were found in another cross-sectional investigation by **Rosen et al. [52]** women with uterine fibroids confirmed by MRI or ultrasound were found to have vitamin D levels below 30 ng/ml, as described in. Our findings were verified by a research showing that 85 percent of women with diagnosed uterine fibroids also had vitamin D deficiency.

A second prospective cross-sectional study of Turkish premenopausal women found that wearing traditional dress, staying at home, and having a low level of education were all factors in an increased risk of vitamin D insufficiency. In addition, the study found that vit D deficiency was more common in women with leiomyoma than In the cases not having the tumor [21].

In addition, According to the results of their examination of the National Health and Nutrition Examination Survey data, **Mitro and Zota [22]** discovered no link between vitamin D and the development of uterine fibroids,

which included 3,590 women with uterine leiomyomata. Inadequate serum vitamin D was linked to considerably greater risks of uterine fibroids in white women, but not in black patients, according to a subgroup analysis of the same data.

Geographical location, latitude, season, weather, clothing, and the usage of sunscreens all play a role in the amount of vitamin D produced in the body in response to sun exposure (in vivo). Fibroids are more common in black housewives because of their dark skin and their tendency to spend time indoors [12, 23].

#### **The strength points of this study:**

The randomized clinical trial design, stringent exclusion and inclusion criteria, and the absence of patients lost to follow-up during the research period are all strengths of this investigation. This is the first study to examine the impact of vitamin-D supplementation on the size of Uterine fibroid in patients with vitamin-D insufficiency, suggesting that doing so may slow the disease's growth and delay the need for more invasive forms of treatment.

#### **The limitations of the study:**

It's important to note that the study has some substantial drawbacks, such as a limited sample size and the fact that the trial was conducted in only one institution rather than being a multicentric study. Another drawback is that it is not a placebo-controlled, double-blind study. Despite the study's shortcomings,

a well-designed trial of vitamin D preparations in uterine fibroids was made possible by the findings. We hypothesized that the therapy we tested would be more effective, safer, and less expensive than current methods of preventing and treating uterine fibroids.

## **5. Conclusion and Recommendations:**

### **Conclusion:**

As evident from the current study, Taking a vitamin D pill is a low-risk method of stabilizing fibroids and preventing them from growing into more serious leiomyomas, both of which can cause significant discomfort. Vitamin D appears to inhibit the development of fibroids.

However, properly designed randomized controlled trials (RCTs) are required to determine whether or whether vitamin D supplementation is effective in preventing or stabilizing the growth of uterine fibroids, as well as the appropriate dosage and duration of such a therapy.

### **Recommendations:**

Serum vitamin D level should be done as routine investigation in diagnosed women with fibroids in the uterus and corrected in case of deficiency which It might prevent the disease from becoming so advanced that standard medical or surgical treatment is required.

Future prospective studies with larger sample sizes are recommended to verify if vitamin D administration is beneficial in preventing or reducing the progression of uterine fibroids.

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