



The Effect of Vitamin D Supplementation on Size of Uterine Leiomyoma in Women with Vitamin D Deficiency

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Abstract

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BACKGROUND: Uterine leiomyomas (fibroids) are the most common benign genital tumors in women. There is a high prevalence of vitamin D deficiency and uterine leiomyomas.

AIM: To evaluate the effect of vitamin D supplementation on the size of uterine leiomyoma in women with vitamin D deficiency.

MATERIALS AND METHODS: It is case-control prospective study which was done in Gynecology Ward at Basrah Maternity and Child Hospital from January 2020 to August 2022. Patients at ages 20–45 years were initially included in the study if they were diagnosed with 1–3 uterine fibroids with a mean diameter ≥ 10 mm. Serum vitamin D levels were estimated for all women before intervention and in those with deficiency of vitamin D (level < 30 ng/mL). Patients with vitamin D deficiency were divided into 2 groups. The 1st group was women who received vitamin D 50,000 cholecalciferol (oral solution) IU weekly for 10 weeks followed by 2000 IU daily for 6–9 month (as study group), while 2nd group received placebo (control group). After the duration of treatment, vitamin D level was estimated and sonography was done to assess the fibroid size at 9–12 months later. In relation to the achievement of normal 25-OH-D3 levels, after the supplementation, the studied population were divided into 2 subgroup of patients: "gave response" and "non-responders" according to their response to treatment.

RESULTS: Vitamin D level was 17.6 (± 3.0) ng/mL and calcium status was 7 mg/dL among 43 females of the study group. Vitamin D level was 34.7 \pm 5 ng/mL after 12 months vitamin treatment ($p < 0.05$). The early vitamin level among 23 control females was 22.4 \pm 7.8 ng/mL in comparison to 24.6 \pm 6.7 ng/mL after 12 months ($p > 0.05$). There was no change for calcium level before and after 12 months period (8.6 vs. 7.9 mg/dL respectively). No changes were noticed among both the study and the control groups as far as the type and position of leiomyoma between the 1st and the 2nd ultrasound after 12 months of therapy.

CONCLUSION: Lower serum vitamin D levels are significantly associated with the occurrence of uterine fibroids.

Introduction

Leiomyomas are common tumors of the female genital system. They have been detected in 20–40% of women during their reproductive years and in up to 70% from the cases after uterine resection [1]. The incidence of fibroid increases with advance age. It was found that 60% of women at the age of 35 years, increasing to 70–80% by the age of 49 years. Malignancy (leiomyosarcoma) occurs at a rate of 0.64/100 000 women/year.

Low parity and infertility appear to be associated with an increased risk of fibroid formation [2]. Polycystic ovarian syndrome is related to leiomyoma, which leads to an increase of gonadotropic hormone and insulin-like growth factor, as beside increase level of androgen [3].

Foods with sugars are associated with an increased risk of fibroid. Women who consume red meat and fish have a higher incidence of fibroids, while those who consume a diet high in fruits and vegetables

have a lower incidence. Numerous studies have also examined the association between arterial hypertension and diabetes mellitus and fibroid risk [2], [3], [4].

Progesterone stimulates fibroid growth, the former through increasing receptors epidermal growth factor and B-cell lymphoma 2 expression while decreasing tumor necrosis factor expression, and the latter by decreasing insulin-like growth factor 1 hormone expression [5], [6]. Vitamin D deficiency has already been demonstrated in a number of gynecological and obstetrical disorders, including infertility and polycystic ovary syndrome [5]. Recent investigations have revealed that vitamin D deficiency as a significant factor in the pathophysiology of fibroid [2], [3], [4], [7], [8], [9]. Vitamin D leads and stopped proliferative effect regardless of mutation status [10].

Vitamin D is thought to be protective against chronic diseases and neoplasms [9], [11]. According to Grant's evaluation, the available scientific data support vitamin D supplementation as a therapy for cancer prevention [12]. Therefore, the aim of this study is to

evaluate the effect of vitamin D supplementation on the size of uterine leiomyoma in women with vitamin D deficiency.

Materials and Methods

Subjects

It is case-control prospective study which was done in Gynecology Ward at Basrah Maternity and Child Hospital and private clinics during January 2020 to August 2022. This research was approved by the ethical Committee of the College of Medicine, Basrah, Iraq, as well as the Arab Board for Medical Specialization. The study included women with uterine leiomyoma which was diagnosed by sonographic examination. Included patients were initially diagnosed with 1–3 uterine fibroids with a mean diameter ≥ 10 mm, confirmed by transvaginal/transabdominal ultrasound.

The inclusion criteria were women at their reproductive age (20–45 years) by estimation of blood FSH level in the 3rd day of menses. Exclusion criteria were pregnant females or had delivery before 6 months, breastfeeding women within 6 months, women with history of myomectomy, with history of loss pregnancy before 24 weeks of pregnancy within 6 months before, usage of hormonal therapy, history of abnormal uterine or difficult reevaluation by ultrasound. Furthermore, women with any type of cancer, all medical diseases, use combined contraceptive pills 3 months before the study.

A careful medical history was taken. Height was taken by scale meter and weight was measured. In this study, we focused on women with uterine fibroid < 50 mm, < 4 fibroids with no fibroid-related symptoms required surgical or medical treatment or had not any concomitant gynecological disease.

Vitamin D estimation: Serum vitamin D levels were estimated for all women. Those with deficiency of vitamin D are considered when vitamin D level < 30 ng/mL [13]. The season was recorded and calcium level was estimated. Patients with Vitamin D deficiency were divided into 2 groups. The first group included women who received vitamin D 50,000 cholecalciferol (oral solution) IU weekly for 10 weeks followed by 2000 IU daily for 9–12 months (study group) [14], while the 2nd group received placebo (control group). After the duration of treatment, vitamin D level was estimated and sonography was done to assess the fibroid size 9–12 months later. Then, the samples were estimated for vitamin D.

In relation to the achievement of normal 25-OH-D3 levels, after supplementation the studied women were divided into 2 samples of patients: "gave response" and "non-responders" according to their response to treatment.

Statistical analysis

The collected data were analyzed by statistical package of SPSS-22. The test of significance was Students *t*-test. The test of significance for percentages was tested using Pearson Chi-square test. Pearson correlation was calculated for the correlation.

Results

During the study period, 473 women underwent a gynecological sonographic examination, 219 of them (47.3%) were diagnosed with uterine fibroids. At the time of initial diagnosis, 16 patients had already vitamin D supplementation and were excluded. The remaining 203 women, regarded as the "initial study population." In those women, the baseline 25-OH-D3, and calcium serum levels were measured. 25-OH-D3 serum level was $24.6 (\pm 9.6)$ ng/mL, the calcium serum level was $8.9 (\pm 0.8)$ mg/dL, and 124 patients were diagnosed with hypovitaminosis D (Table 1).

Table 1: Vitamin D and calcium serum levels and fibroids characteristics in both study and control group

Characteristics	Before treatment	After 1 year	p-value
Study group (n = 43)			
Vitamin D level	17.6 ± 3	34.7 ± 5	0.001
Ca+2 level	7.7 ± 2	7.9 ± 7	0.5
Fibroid diameter (mm)	18 (1.7–28.4)	19 (15–32)	0.3
Fibroid volume (cm ³)	7.9 (2.8–31)	8.1 (2.3–31)	0.5
Control group (n = 23)			
Vitamin D	22.4 ± 7.8	24.6 ± 6.7	0.12
Ca level	8.7 ± 0.6	7.9 ± 1.2	0.5
Fibroid diameter	23 (20–34)	28 (22–34)	0.02
Fibroid volume (cm ³)	8.6 (4.2–21)	11.5 (5.5–22.4)	0.01

No difference in the season during sample collection (48.1% autumn–winter vs. 51.9% spring–summer ($p = 0.42$)). A significant difference in the mean 25-OH-D3 serum level between women with hypovitaminosis D ($n = 124$) and the women with normal vitamin D serum levels ($n = 79$) was reported (20.4 ± 5.9 vs 39.0 ± 8.0 ng/mL ($p < 0.001$)). For all women who were diagnosed with hypovitaminosis D, a standard vitamin D supplementation therapy [15] was offered, routinely.

The initial population study revealed that 124 women with uterine fibroids and hypovitaminosis, 53 out of 107 constituted the small burden disease performed the therapy adequately which regard study group, 3 women got pregnant and 7 women underwent traditional treatment while the remaining 43 had adequate therapy. Of the 54 control women with uterine fibroid and without vitamin D supplementation, 4 get pregnant during the follow-up and 26 underwent treatment 24 were the remaining control group.

The remaining 43 women in the "study group" and 24 in the "control group" underwent an ultrasound evaluation and a 25-OH-D3 and calcium serum levels determination (12 months after the initial diagnosis). No

sign of vitamin D toxicity was reported in any patient (Table 1).

Vitamin D, calcium serum levels, and fibroids characteristics in the study group (43 women, with a total of 71 fibroids) and the control group (23 women, with a total of 68 fibroids) at the beginning of the study and after 1 year.

Considering the 43 women of the “study group” for which the call-back visit was performed, the mean (\pm SD) baseline 25-OHD3 serum level was 17.6 (\pm 3.0) ng/mL, and for calcium serum level was 7.7 (\pm 2.0) mg/dL. At the call-back visit (performed 12 months after the starting of appropriate vitamin D supplementation therapy), the mean 25-OH-D3 serum level in those women was 34.7 \pm 5 ng/mL ($p < 0.001$) (Table 1).

In the 23 women of the “control group” for which the call-back visit was performed, the mean (\pm SD) baseline 25-OH-D3 serum level was 22.4 \pm 7.8 ng/mL. At the call-back visit (performed 12 months after the initial diagnosis), the mean 25-OH-D3 serum level was 24.6 \pm 6.7 ng/mL; with non-significant relationship. In these 23 women, the mean (\pm SD) and calcium serum levels measured 12 months after the initial diagnosis were not significantly different from baseline levels 8.6 \pm 0.6 versus 7.9 \pm 1.2 ($p = 0.15$), respectively (Table 1).

The number, site, and location of all fibroids remained the same between the initial and the final ultrasound after 1 year of therapy both in the “study group” and in the “control group.” A significant increase in fibroids diameter and volume was found in women of the “control group” ($p < 0.001$), while no significant difference in diameter or volume of fibroids emerged in women of the “study group” (Table 1).

1 year after the initial diagnosis, considering the 43 women of the “study group” for which the call-back visit was performed, 19 patients (41.9%) reached normal levels of 25-OH-D3 (responders), while 24 (58.1%) did not reach a normal level (non-responders), with no significant difference between the two groups in background or clinical characteristics (Table 2).

Table 2: Background and clinical characteristics in the study group (responders and non-responders)

Characteristics	Responders (n = 19)	Non-responders (n = 24)	p-value
Age (years)	33.5 \pm 4	35.3 \pm 3.1	0.16
BMI (kg/m ²)	28.5 \pm 4.7	29.4 \pm 2.1	0.8
Smoking	0	0	
Comorbidities			
Hypertension	4	1	0.01
Diabetes	0	0	0
Hypothyroidism	1	2	0.3
Obstetrics and gynecological history			
Infertility	0	0	
Parity	1.5 (1–3)	2 (1–5)	
Abortions	3 (2–4)	2 (1–3)	
Previous myomectomy	1	0	

The “responders” had a baseline 25-OH-D3 serum level of 20.3 \pm 7.4 ng/mL and then 40.1 \pm 9.1 ng/mL after 1 year of therapy ($p < 0.001$). The “non-responders” had a starting 25-OH-D3 level of

19.6 \pm 6.7 ng/mL and a final level of 23.9 \pm 4.7 ng/mL ($p = 0.02$) (Table 3).

Table 3: Fibroids characteristics in responders and non-responders

Characteristics	Responders (n = 19)	Non-responders (n = 24)	p-value
Number of fibroids	1 (1–3)	1 (1–4)	0.63
Initial diameters (mm)	18 (15–35)	19 (16–33)	0.76
Initial volume (cm ³)	8 \pm 5 (2–10.5)	7.1 (2–19)	0.87
Final diameter	16 \pm 2	8 \pm 4	0.05
Final volume	8 \pm 2 (2–8.5)	10.4 (2–19)	
Initial level of vitamin D (ng/mL)	20.3 \pm 7.4	19.6 \pm 6.7	0.2
Final level of Vitamin D	40.1 \pm 9.1	23.9 \pm 4.7	0.02

Discussion

Hypovitaminosis D has recently been associated with higher prevalence of uterine fibroids. There is a relation between low level of Vitamin D and uterine leiomyoma. Furthermore, it was reported that there is an inverse relation between serum vitamin D serum levels and the size of uterine fibroids [16]. Previous study has reported a higher expression of vitamin receptors in fibroids than in normal myometrium [17]. Hence, vitamin D plays a role in regulating fibroid growth or differentiation [18].

It has been demonstrated that vitamin D inhibits the growth of fibroid cells through the down-regulation of proliferating cell nuclear antigen, cyclin-dependent kinase 1, and B-cell lymphoma 2 (and suppresses the catechol-O-methyl transferase expression and its activity) [19]. In addition, vitamin D seems to reduce the transforming growth factor beta-3 effects on the process of fibrosis in human fibroid cells and to limit the aberrant expression of major extracellular matrix-associated proteins [15]. Moreover, it has been found that treatment with 1,25-OH-D3 significantly reduces fibroid tumor size in Eker rats by suppressing cell growth and proliferation-related genes, antiapoptotic genes, and estrogen and progesterone receptors [20]. These data are of particular clinical relevance since vitamin D could be a potential safe, non-surgical therapy for the treatment of uterine fibroids [21].

In this study, it was suggested that 25-OH-D3 is effective in restoring normal levels of vitamin D in women with uterine fibroids. After 1 year of therapy, the mean level of 25-OHD3 in the study group was significantly higher compared with the baseline level (30.7 \pm 10.5 vs. 19.9 \pm 7.0 ng/mL ($p < 0.001$). Moreover, the efficacy of supplementation seems to be related to the baseline vitamin D serum levels, with higher responses in women with lower levels at the time of initial diagnosis. This finding appears to be consistent with previous study [13]. Therefore, according to the present results, in the presence of uterine fibroids does seem to affect the response to vitamin supplementation. The women who underwent an appropriate supplementation therapy, there

were high response to vitamin D level in about 90% which is in agreement with other studies which was 89% [20]. While it was found in other work low response about 5% [19]. It was reported that serum 25-OH-D3 response to vitamin D supplementation could be related to genetic factors, body mass index, and baseline levels [19]. Anyhow, the potential impact of uterine fibroids on the effectiveness of vitamin D supplementation is currently unknown.

In the present, we did not find any significant differences in background and clinical characteristics between “responders” and “non-responders.” Moreover, the failure to achieve normal levels of vitamin D seems not to be related to the characteristics of uterine fibroids. Hence, additional genetic factors could be involved and should be properly investigated in future studies, to identify patients with lower response to 25-OH-D3 supplementation.

Analyzing the potential effects of vitamin D supplementation on uterine fibroids, we noted among the women with “small burden” disease and hypovitaminosis D who performed an adequate vitamin D supplementation (study group), a lower rate of “progression to extensive disease,” with the need of surgical or medical treatment, was observed in the 12 months after the initial diagnosis. This could mean that women with uterine fibroids who underwent vitamin D supplementation had a lower risk of progression of uterine disease. The effect of vitamin D supplementation was comparing the sonographic features of uterine fibroids in the beginning and 12 months after the initial diagnosis, both in patients who had properly performed the therapy (study group) and in those who did not adequately perform the therapy (control group). No significant differences were found in diameter or in volume of the identified fibroids in the study group, while a slight but significant increase in diameter and volume was noted in the control group. Thus, the growth pattern of fibroids with “small uterine burden” under supplementation with 25-OH-D3 seems to be stable, with no increases or decreases in size or number of identified lesions. Instead, women with “small burden” uterine fibroids who did not perform appropriate vitamin D supplementation seem to have a slight but significant increase in size of the lesions and a higher need for subsequent medical or surgical therapy. A recent reviews have reported that women in the perimenopausal period should be considered to have a higher risk of developing fibroids [21], [22]. Moreover, immediately before menopause, women can experience several months or years of estrogen-dominated menstrual cycles, with a risk of a growth spurt of fibroids, considering their estrogen sensibility [22]. Given this fact, the effect of vitamin D supplementation on the size and number of “small burden” uterine fibroids could be most beneficial, especially in pre and perimenopausal women.

Growth of fibroids and the onset of fibroid-related symptoms and the possible beneficial

effects of vitamin D supplementation in women with hypovitaminosis D might become evident with longer duration of therapy or with different dosages of 25-OH-D3. However, additional studies are needed.

However, our results could represent a starting point for future bigger and well-designed trials. The small sample size is another potential limitation of this study as well as the potential inaccuracy of the sonographic method of evaluation and measurement of fibroids, which inevitably has an ultrasound-related degree of imprecision. However, all ultrasound examinations were performed by the same senior sonographer, and we used a standard technique for the identification and measurement of fibroids.

However, appropriate and well-designed randomized controlled trials will be desirable, to confirm the effectiveness of vitamin D supplementation in inhibiting or stabilizing the growth of uterine fibroids, and to better clarify the optimal dosage and duration of such a therapy.

Conclusion

According to the present study, lower serum vitamin D levels are significantly associated with the occurrence of uterine fibroids. There is an inversely correlation with both uterine fibroids, volume, and low level of vitamin D. It showed that administration of vitamin D may reduce the size of leiomyoma. This is the first evaluation of an “*in vivo*” effect of vitamin D supplementation in women with uterine fibroids, which confirms the hypothesis that it could be a safe, low-cost, and low-risk treatment for fibroids stabilization, preventing the progression to more severe and symptomatic conditions. Hence, to investigate the potential role of vitamin D supplementation therapy in women with uterine fibroids, appropriate well-designed randomized controlled trials should be performed.

Ethics

This study was approved by the Ethical Committee of the College of Medicine, University of Basrah, Basrah, Iraq, as well as the Arabic Board of Medical Specialization.

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