

EFFECT OF VITAMIN D SUPPLEMENTATION ON THE SIZE OF UTERINE FIBROIDS**Dr. Shiuly Chowdhury*¹, Dr. Minhazul Islam², Dr. Shuva Shrestha³ and Dr. Shahjada Selim⁴**¹Associate Professor, Department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University Dhaka, Bangladesh.²Assistant Professor, Department of Radiology and Imaging, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.³Department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.⁴Associate Professor, Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.***Corresponding Author: Dr. Shiuly Chowdhury**

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ABSTRACT

Background: Uterine fibroids are benign smooth muscle tumors of the uterus. There is a high prevalence of vitamin D deficiency in patients with uterine fibroids. However, the impact of vitamin D on the reduction of the size of the uterine fibroid is still unknown. **Objective:** The objective of this study was to determine the effect of vitamin D supplementation on the size of uterine fibroids. **Materials and Method:** A total of 47 participants diagnosed as uterine fibroids (size less than 5 cm) were included in the study. The size of the fibroid was determined by ultrasonography. Baseline vitamin D investigation was done to assess the level of vitamin D. Then vitamin D was supplemented to the participants for three months and repeat ultrasonography was done at 3 months. Regression of the size of fibroid was also done. **Results:** The mean age was 37.6±8.2 years. Mean vitamin D was 20.32±8.03. According to fibroid size <3cm (small), 3-3.9 cm (medium) and 3.9-4.9 cm (large) at the initial stage was 36.2% (n=17), 48.9% (n=23) and 14.9% (n=7) participants, respectively. After vitamin D supplementation, it became 61.7% (n=29), 31.9% (n=15) and finally 6.4% (n=3). The mean size of fibroids was 3.26±0.74 and after vitamin D supplementation it had been reduced to 2.85±0.78. Furthermore, we found that, according to vitamin D status of deficiency (<20), insufficiency (20-29.9), and sufficiency (≥30) all mean value of follow up fibroids were significantly reduced. **Conclusion:** Vitamin D supplementation in women helps regress the size of uterine fibroids and it is more effective in small sizes.

KEYWORD: Uterine fibroid (UF), vitamin D, 25[OH] D.**INTRODUCTION**

Uterine fibroids are benign growths that develop from the muscle tissue of the uterus.^[1,2] They are also called leiomyomas or myomas. Furthermore, the size, shape, and location of fibroids can vary to a great extent that they might be appeared inside of the uterus, on its outer surface or within its wall, or attached to it by a stem-like structure. Moreover, a woman may have only one fibroid or many of varying sizes. They may also remain very small in size for a long time but suddenly they grow rapidly or grow slowly with an increase of the time. Usually, they are more common in women aged 30–40 years, but they can occur at any age. However, several studies have reported that it can occur more often in African American women than in white women and at a younger age, they grow more quickly in African American women.^[3,4] Regarding the clinical symptoms, it is indicated that small uterine fibroids are rarely associated with symptoms. Occasionally, uterine fibroids may be complicated by a variety of symptoms, including

menstrual disturbance, pressure symptoms, bloated sensation, increased urinary frequency, bowel disturbance, or pelvic pain.^[5,6] Therefore, definite treatment methods are essential according to the symptoms and condition of the patients. The diagnosis of fibroids can be performed with clinical pelvic examination, and/or abdominal and transvaginal ultrasound and other imaging modalities. Although, it appears as well-defined, hypoechoic masses that might cause a variable amount of acoustic shadowing in the ultrasonography, depending on the level of calcification or/and the amount of fibrous tissue, leiomyomas may present different echogenicity, usually hyperechogenic or isoechoic.^[5,6] The treatment of fibroids is mainly surgical such as a hysterectomy (abdominal and vaginal) and myomectomy as conservative surgery. This is always related to hospitalizations of the patient and morbidity.^[7,8] However, many women want to preserve the uterus for the reproductive future. In that situation, different drugs such as selective progesterone receptor

modulator, gonadotropin-releasing hormone analogs, etc. are indicated to control heavy bleeding, painful periods.^[9] The relation between Vitamin D and fibroids are also studied. The sources of vitamin D mainly comes from ultraviolet B ray via the skin (80%) and the remaining 20% from their diet. The synthesis of vitamin D is also investigated. It has been reported that sunlight transforms 7-dehydrocholesterol into the pre-vitamin D₃, which is then changed to vitamin D₃. When vitamin D is taken to the liver and it is transformed into 25-hydroxyvitamin D (25[OH]D or calcidiol), which is the major circulating metabolite.^[10,11] Again, from the liver, the 25[OH] D travels to the kidneys where it is converted into 1, 25-dihydroxy vitamin D (1, 25[OH]2D or calcitriol), which is the active form of vitamin D. This renal conversion is keeping up by plasma parathyroid hormone levels, as well as serum calcium and phosphorus levels. However, the metabolite 25[OH]D is currently the chosen serum level and is considered as a more accurate indicator for the vitamin D status than 1, 25[OH] D. Therefore, vitamin D deficiency is defined most commonly as a 25(OH) D level < 20 ng/mL. On the other hand, vitamin D insufficiency is described as 21 to 29 ng/mL, while anyone with a vitamin D ≥30 ng/mL is considered as sufficient. Vitamin D intoxication can occur with a 25[OH]D level > 150 ng/mL.^[10,11] There is a positive relationship between vitamin D deficiency and uterine fibroids. Among the Turkish and African-American population, there is a positive uterine leiomyoma and vitamin D relationship.^[12,3] Furthermore, calcitriol treatment of human uterine fibroid tissue may reduce the cell proliferation, and thereby inhibit molecular pathways for fibrosis.^[1] These studies also revealed that the vascular and airway smooth muscle may also show similar anti-proliferative responses to calcitriol, and the anti-fibrotic effects have also been observed in the kidney. Furthermore, vitamin D has functional effects including decreased cell proliferation, increased apoptosis, and differentiation, regulation in biological pathways. Other studies have indicated that a positive feedback mechanism on extracellular matrix and cell proliferation plays a role in fibroid pathogenesis which may be inhibited by vitamin D.^[12] Several in vivo and in vitro studies have found that both myometrium and leiomyoma cells had high sensitivity for the regulatory effect of vitamin D. In the cell culture studies; Barakta et al.¹³ reported that a dose of 1,25(OH)D₃ is sufficient to slow down the cell growth of leiomyoma and myometrium. Furthermore, vitamin D might inhibit the growth of leiomyoma cells causing an anti-estrogenic effect.^[14] Moreover, the proliferative effect induced by TGF-β₃ (transforming growth factor) was decreased by vitamin D.^[15] A previous study has indicated that a dose of 1.25(OH)D₃ is competent to encourage shrinkage in leiomyomas by repressing cell proliferation and apoptotic protein expression that reduced the estrogen and progesterone receptors and type-1 collagen expression.^[16] This is also supported by some of the previous studies that vitamin D can inhibit uterine fibroid

growth as a potent anti-tumor agent.^[17,18] Based on the previous studies, it can be considered that vitamin D supplements may also be effective in the reduction of the size of the fibroid. However, there is still no definitive study has been performed to investigate whether vitamin D can be used for small size fibroids without major symptoms. Therefore, the purpose of the present study was to determine the effect of vitamin D supplementation on the size of uterine fibroids.

MATERIALS AND METHOD

This interventional study has been conducted from July to September 2019 in the department of obstetrics & gynecology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, and the participants were women who attending the outpatient department (OPD) of BSMMU having a radiological diagnosis of fibroid uterus (size < 5 cm in diameter). Finally, a total 47 participants had been recruited who fulfilled the inclusion criteria and signed the informed consent form. Participants with heavy menstrual bleeding (>80.0 mL), pelvic discomfort, severe anemia, infertility, or other indications for surgery, complicated with myoma degeneration and adenomyosis, malabsorption syndrome, planning of pregnancy in near future, acute crisis, history of the previous myomectomy, history of total thyroidectomy, chronic systemic disease, any malignancy, menopausal women, pregnant and lactating women, history of or current vitamin D replacement, abortion and pregnancy loss in the past 6 months and oral contraceptive/hormonal agents used in the past three months were excluded from the study. Socio-demographic, personal habits, and family information were collected by face to face interview and disease-specific data were recorded from the register. Bodyweight, height, waist circumference was also recorded. Then vitamin D was supplemented in the prescribed dose among the participants. Then repeat ultrasonography was done after 3 months, to assess the impact of vitamin D on the regression of the size of the fibroid. The purpose and procedure of the study were discussed with the participants and the ethical committee clearance was obtained from the institution. Vitamin D₃ was measured by high-performance liquid chromatography (HPLC) method.

RESULTS

Table- 1 showed that, according to patient's age group highest number of participants, 31 (66.0%) were from 31-45 years' age group. The mean age of the participants was 37.6±8.2 years. According to the educational status, the highest 14 (29.8%) were higher secondary level educated followed by 13 (27.7%) completed secondary level education. Majority of the participants were housewives 33 (70.3%), followed by 5 (10.6%) service holders. Regarding patient's marital status, 45 (95.7%) were married and 2 (4.3%) unmarried.

Table 1: Socio-demographic characteristics of the participants.

Characteristics	Frequency (N=47)	Percentage (%)	Mean±SD
Age in Years			
20 – 30	10	21.2	37.6±8.2
31 -45	31	66.0	
>45	6	12.8	
Education			
Illiterate	3	6.4	
Primary	12	25.5	
Secondary	13	27.7	
Higher secondary	14	29.8	
Graduate or Above	5	10.6	
Occupation			
House wife	33	70.3	
Service	5	10.6	
Student	4	8.5	
Others	5	10.6	
Residence			
Urban	25	53.2	
Rural	22	46.8	
Monthly Family Income			
10,000-20,000	16	34.0	29489±12848
21,000-30,000	18	38.3	
>30,000	13	27.7	
Marital Status			
Unmarried	45	95.7	
Married	2	4.3	
Widow/Divorce	0	0.0	
No Children(Parity)			
0	9	19.1	
1	8	17.0	
≥2	30	63.8	
Base	47	100.0	

Table 2 showed that, after vitamin D supplementation, the frequency of small size fibroid (<3cm) increased from 17(36.2%) to 29(61.7%), but the medium size (3-3.9cm) & large size (>3.9-4.9cm) fibroid patient's

frequency didn't increased. The total mean (±SD) value fibroid was 3.26±0.74 and after having vitamin D fibroid mean was 2.85±0.78. BMI 28.22±4.71.

Table 2: Clinical characteristics of the participants.

Characteristics	Frequency (N=47)	Percentage (%)	Mean ±SD
Fibroid Size			
Small (<3cm)	17	36.2	3.26±0.74
Medium (3-3.9cm)	23	48.9	
Large (>3.9-4.9cm)	7	14.9	
Follow up Fibroid Size			
Small (<3cm)	29	61.7	2.85±0.78
Medium (3-3.9cm)	15	31.9	
Large (>3.9-4.9cm)	3	6.4	
BMI			
Under weight	1	2.1	28.22±4.71
Normal	11	23.4	
Over weight	19	40.4	
Obese	16	34.0	
Base	47	100.0	

Table 3 showed that, higher number of patients had vitamin D insufficiency; 24(51.1%) and mean value of

20.32±8.03. The participant's age was 31-45 years and the highest number 9(52.9%) belongs to vitamin D

insufficiency. Regarding vitamin D status, the mean value of age groups 20-30 years was 20.9±8.1, 31-45

years was 21.2±8.2 and >45 years 14.8±5.9 respectively. The p-value was 0.822.

Table 3: Different Vitamin D status and relation with different age group of the participants.

Characteristics	Frequency (N=47)		Percentage (%)		Mean ±SD	
Vitamin D Status						
Deficiency (<20)	17		36.2		20.32±8.03	
Insufficiency (20-29.9)	24		51.1			
Sufficiency (≥30)	6		12.8			
Base	47		100.0			
Age Group	Vitamin D					
	Deficiency (<20)		Insufficiency (20-29.9)		Sufficiency (≥30)	
	n	%	n	%	n	%
20 - 30	4	23.5	4	16.7	2	33.3
31 -45	9	52.9	18	75.0	4	66.7
>45	4	23.5	2	8.3	0	0.0
Base	17	100.0	24	100	6	100.0
Age Group	Vitamin D Level					
	Frequency (N=47)	Mean ±SD	95% Confidence Interval		p-Value	
			Lower Bound	Upper Bound		
20 – 30	10	20.9±8.1	18.18	25.06	0.822 ^{ns}	
31 -45	31	21.2±8.2	20.39	23.96		
>45	6	14.8±5.9	12.52	23.92		

- ns= not significant

Table 4 stated that, after serving vitamin D fibroids mean value size were changed in all three vitamin D status of deficiency (<20), insufficiency (20-29.9) and sufficiency

(≥30). And it depicted more significant in vitamin D insufficient group (p=0.0008) and sufficiency group (p=0.0001).

Table 4: Uterine fibroids size changes according to vitamin D status of the participants.

Characteristics	Vitamin D								
	Deficiency (<20)			Insufficiency (20-29.9)			Sufficiency (≥30)		
	n	Mean ±SD	p-Value	n	Mean ±SD	p-Value	n	Mean ±SD	p-Value
Fibroid	17	3.2±0.8	0.2286 ^{ns}	24	3.4±0.7	0.0008 ^s	6	2.9±0.7	0.0001 ^s
Follow up Fibroid	17	3.0±0.8		24	2.9±0.7		6	2.3±0.7	

ns= not significant, s= significant

Table 5 stated that, according to fibroid mean value size were reduced in medium (3-3.9cm) from 1.9±0.6 to 1.7±0.6, large (>3.9-4.9cm) 1.6±0.5 to 1.3±0.6 rather

than small size (<3cm) of fibroid. And it depicted that the reduction of uterine fibroid size was significant in larger size (3.9-4.9cm) (p= 0.0099)

Table 5: Uterine fibroids size changes after vitamin D supplementation in different fibroid size- groups.

Characteristics	Vitamin D								
	Small (<3cm)			Medium (3-3.9cm)			Large (>3.9-4.9cm)		
	n	Mean ±SD	p-Value	n	Mean ±SD	p-Value	n	Mean ±SD	p-Value
Fibroid	17	1.7±0.8	0.2003 ^{ns}	23	1.9±0.6	0.1095 ^{ns}	7	1.6±0.5	0.0099 ^s
Follow up Fibroid	29	1.9±0.7		15	1.7±0.6		3	1.3±0.6	

ns= not significant, s= significant

Table 6 stated that, the correlations among vitamin D and fibroid. Follow up patients was all most zero (0.32) correlated with vitamin D and p-value was 0.026

Table 6: Correlation's between uterine fibroids and follow up fibroids after vitamin D supplementation among the participants.

Characteristics	Vitamin D	
	r	p- Value
Fibroid	1	0.026
Follow up Fibroid	0.32	

- ns= not significant, s= significant
- P value has been calculated on the mean sizes of fibroids.

DISCUSSION

Although there were no studies have been performed on the impact of vitamin D supplementation on the sizes of the uterine fibroids but several studies have been performed on the relation between vitamin D deficiency and uterine fibroids. The present study revealed that at the initial stage, 36.2% (n=17) participants had small size of UFs (<3 cm), 48.9% (n=23) medium (3-3.9 cm) and 14.9% (n=7) large size UFs (4.0–4.9 cm), respectively. The mean size of fibroids of total 47 participants was 3.26±0.74 cm and after vitamin D supplementation it had been reduced to 2.85±0.78 cm. These findings are similar with a study that lower serum Vitamin D levels are inversely correlated with UFs in different ethnic groups. Therefore, it can be considered that vitamin D deficiency is a possible risk factor for the occurrence of UFs. The mean level of serum 25-OH Vitamin D, plus or minus standard deviation, was found to be significantly lower in cases with UFs (19.7±11.8 ng/mL) than in healthy controls (22.3±6.5 ng/mL) (P=0.01).^[19] Furthermore, several studies have been performed on the relation between vitamin D deficiency and uterine fibroids. Among the Turkish population, there is a positive uterine leiomyoma and vitamin D relationship.^[12] In African-American populations, there is a positive correlation between vitamin D deficiency and presence of uterine fibroids.^[3] However, the results of the present study are also consistent with data showing a protective effect of treatment with calcitriol on fibroids in an animal model of fibroid. In addition, calcitriol treatment of human uterine fibroid tissue reduces cell proliferation, and inhibit molecular pathways for fibrosis.^[16] The reasons of the reduction of the fibroid size following vitamin D supplementation are not clarified in the present study. However, several hypotheses had been proposed. A study revealed that vitamin D has the capability to decrease cell proliferation, increased apoptosis, differentiation or regulation in biological pathways.^[20] Other studies have indicated that extracellular matrix and cell proliferation plays a role on fibroid pathogenesis which may be repressed by vitamin D.^{21,22} Furthermore, several studies have found that both myometrium and leiomyoma cells had high sensitivity for the regulatory effect of vitamin D. A dose of 1,25(OH)D₃ is sufficient to inhibit the leiomyoma and myometrial cell growth or it may slow down the growth of leiomyoma cells and the proliferative effect induced by TGF-β₃ (transforming growth factor) which is repressed by vitamin D causing an anti-estrogenic effect.^[23,24] In a study of Ciavattini *et al.*^[25] revealed a significant increase in the 25-OH-D₃ serum level 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 of conventional surgical or medical therapy.^[25] Other treatment option includes clinically symptomatic uterine fibroids are most often treated with surgery. Various types of surgical methods are available, both open and endoscopic (hysterectomies and myomectomies).^[7,8] However, in the present study, all afford was taken to reduce the size of the fibroid by using vitamin D supplement. One study has indicated that reducing blood loss and tumor burden could be a good option to preserve the fertility.^[26] Women who wish to keep their uterus can be treated with less invasive methods because the surgical method sometime requires a re-intervention in the future. Therefore, to reduce the morbidity and risk of adverse effects, Vitamin D supplement was used to reduce the size of the fibroids and it was found that vitamin D supplementation is capable of reducing the size of small fibroid. However, it is still unknown whether or not vitamin D supplementation is effective in reducing the size of large tumor. Therefore, further research is needed to confirm the results found in the present study.

CONCLUSION

It can be concluded that vitamin D supplementation might be an effective, safe and low-cost therapy in the primary prevention and treatment of uterine fibroids, but its efficacy in humans needs to be carefully evaluated.

Ethical Issue

This research was approved by the Institutional Review Board of Bangabandhu Sheikh Mujib Medical University (Ref. no. BSMMU/2019/3892).

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Conflict of Interest

Authors declare no conflict of interest.

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