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Original Article

Vitamin D Deficiency in Premenopausal Women and Impact of its Replacement Therapy on Uterine Fibroid Growth

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Abstract

Objective: To ascertain the average change in fibroid size in women who are vitamin D deficient following vitamin D supplementation.

Methodology: This Quasi experimental trial was conducted at Department of Obstetrics and Gynecology, Sir Ganga ram hospital, Lahore from 18th July 2022 to 17th January 2023. A total of 115 premenopausal women between 40 and 45; vitamin D deficiency proven by laboratory analysis; women with uterine fibroids of size less than 5 centimeter on ultrasound were included. Patients who have had vitamin D supplementation in the last 1 year; women taking regular calcium and vitamin D daily supplementation; pregnant or lactating women; women with autoimmune disorders, endocrinopathies, malignancy or on-going infectious disease; history of prior myomectomy or intervention for fibroids were excluded. Vitamin D 2 lac unit injection supplementation, once weekly for 12 weeks per orally was given. At the start of the study, all women had an ultrasound that measures the size and volume of the uterine fibroid and vitamin D level was checked.

Results: In my study, mean fibroid size at baseline and post-treatment was 34.23 ± 9.66 mm and 27.18 ± 9.39 mm respectively (p-value <0.0001). In women who were vitamin D deficient, the mean change in fibroid size following vitamin D supplementation was 6.79 ± 1.98 mm.

Conclusion: This study found that vitamin D supplementation decreases fibroid size in women who are vitamin deficient.

Keywords: Uterine Fibroid, Vitamin D Deficiency, Vitamin D Supplementation.

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Introduction

Leiomyomas, another name for uterine fibroids, are monoclonal diploid gynecological tumors that originate from the smooth-muscle tissue of the uterus.[1] The overproduction of extracellular matrix (ECM) is one of its characteristics.[2] With a prevalence ranging from 5.4% to 77%, they are the most prevalent benign pelvic tumors in women who are of reproductive age.[3]

Uterine fibroids are associated with a number of risk factors, both modifiable and non-modifiable. These include factors including age, race, endogenous and exogenous hormones, obesity, uterine infections, nulliparity, and lifestyle choices that can be changed, such as stress, smoking, physical activity, nutrition, coffee, and alcohol.[4]

Urinary retention, pelvic discomfort, heavy menstrual bleeding, and intermenstrual hemorrhage are common symptoms of fibroids. Moreover, early pregnancy loss and subfertility are linked to fibroids.[5]

Mifepristone, gonadotropin-releasing hormone analogs, and oral contraceptives are examples of traditional medical treatments. With encouraging results, ulipristal acetate, a novel selective progesterone receptor modulator, was first used to treat uterine fibroids.[6] When circumstances allow, women with bothersome fibroids are frequently treated medically before undergoing surgery. Surgical management includes myomectomy and hysterectomy and minimally invasive techniques have also been developed such as selective angio-embolisation of the uterine artery to occlude the feeder vessels to the fibroid.[7]

Although Pakistan has a sunny climate and a subtropical location, vitamin D deficiency has been

found to be widespread, particularly among women. According to a recent study, 90% of premenopausal females had blood 25-hydroxyvitamin D (2510H] D) values <50 nmol/L (20 ng/mL).[8] Munusamy et al., have reported 78% prevalence of uterine fibroids in Pakistani women.[9] Lastly, a study found that the mean change in size of fibroids over 6 months with and without vitamin D supplementation was 7.14 S.D 3.86 and -0.28 S.D 1.98, showing that vitamin D did indeed decrease uterine size whereas non supplementation lead to an increase in size of the fibroid.[10]

Interestingly, a study by Blauer et al. discovered that vitamin D replenishment may slow the growth of fibroids, reducing the need for surgery, which is crucial for premenopausal women. This was further reiterated in a study done by Corachan et al, the hypothesis being that modulation of transforming growth factor-beta by vitamin D plays a significant role in regulating appropriate cell cycle death and unchecked growth thus limiting the proliferation, fibrosis and increase in size commonly seen in fibroids.[10]

Therefore, we aim to conduct a quasi-experimental trial to establish the effect of vitamin D replacement therapy on uterine fibroid growth both of which commonly co-exist in Pakistan's population. The study would enable decreasing surgical intervention in women for symptomatic fibroids and saving them from unnecessary surgery if we find that Vitamin D replacement therapy significantly decreases the size of uterine fibroids.

Methodology

This quasi-experimental study was conducted in the Department of Obstetrics and Gynecology, Sir Ganga Ram Hospital in Lahore, from July 2022 to January 2023 after being approved by the ethical review committee. The mean change in fibroid following vitamin D treatment is 7.14 ± 3.86, with a 95% confidence level, absolute precision of 0.07, and a minimum sample size of 115 cases.[10] All pre-menopausal women between the age of 40 to 45; vitamin D deficiency proven by laboratory analysis (less than 20 ng/ml); women with uterine fibroids of size less than 5 centimeter on ultrasound were included. Women who have had vitamin D supplementation in the last 1 year; women taking regular calcium and vitamin D daily supplementation; pregnant or lactating women; women with autoimmune disorders, endocrinopathies, malignancy or on-going infectious disease; history of prior myomectomy or intervention for fibroids were excluded.

Patients were given NSAIDS, Paracetamol and combined oral-contraceptive pills as standard conservative management for fibroids. Vitamin D 2 lac unit injection supplementation, once weekly for 12 weeks per orally was given. At the start of the study, all women had an ultrasound that measures the size and volume of the uterine fibroid and vitamin D level was checked. After starting the study, all women had a follow up ultrasound for size and volume of fibroid and vitamin D level at 8 weeks, 12 weeks, 16 weeks and 24 weeks. This serially measured the size of the uterine fibroids at each follow up in centimeters with the length of the fibroid being used as the dimension of measurement. Women whose vitamin D level on follow up reaches 20-50ng/m1 were given maintenance therapy of 1000 IU oral vitamin D till the end of the study to avoid intoxication of vitamin D.

SPSS version 24 was used to enter and analyze all of the data that was gathered. For numerical factors including age, symptom duration, BMI, and fibroid size (pre, post, and change), mean and standard deviation were computed. For each type of fibroid, frequency and percentages were computed. The data was stratified by age, BMI, duration, and fibroid type. Following stratifications, an independent "t" test was used, with $p \leq 0.05$ being considered statistically significant.

Results

Mean age was 42.74 ± 1.61 years. Majority of the females i.e. 66 (57.39%) were between 43 to 45 years of age. Mean duration of disease was 8.08 ± 3.08 months (Table IV). Mean BMI was 25.30 ± 4.48 kg/m2. Distribution of patients according to different variables is shown in Table 1.

In my study, mean fibroid size at baseline and post-treatment was 34.23 ± 9.66 mm and 27.18 ± 9.39 mm respectively (p-value <0.0001). According to Table 2, the mean change in fibroid size in women with vitamin D deficiency following vitamin D supplementation was 6.79 ± 1.98 mm.

Stratification of mean change in fibroid size with respect to confounding variables is shown in Table III.

Discussion

Numerous studies have demonstrated that vitamin D

Table 1: *Distribution of different variables (n=115).*

Variables		No. of Patients	%age
Age (years)	40-42	49	42.61
	43-45	66	57.39
Duration (months)	≤9	83	72.17
	>9	32	27.83
BMI (kg/m^2)	≤25	79	68.7
	>25	36	31.3
Type of fibroid	Subserosal	77	66.96
	Intramural	38	33.04

Table 2: *Mean change in fibroid size after vitamin D Supplementation in Vitamin D deficient women*

Variables	Fibroid size		p-value
	Mean	SD	
Pre-treatment	34.23	9.66	0.0001
Post-treatment	27.18	9.39	
Change	6.79	1.98	

Table 3: *Stratification of change in fibroid size with respect to age groups*

Variables		Change in fibroid size		P-value
		Mean	SD	
Age (years)	40-42	7.08	1.86	0.074
	43-45	6.41	2.1	
Duration (months)	≤9	7.06	2.01	0.019
	>9	6.09	1.75	
BMI (kg/m^2)	≤25	6.49	1.87	0.003
	>25	7.78	2.06	
Type of fibroid	Subserosal	6.86	1.88	0.615
	Intramural	6.66	2.21	

reduces cellular proliferation, increases apoptosis, promotes differentiation, and regulates a wide range of other basic tissue-level activities, including vascular angiogenesis, extracellular matrix production, and other immunological mechanisms.[11]

I have conducted this study to determine the mean change in fibroid size after vitamin D Supplementation in Vitamin D deficient women. In my study, mean fibroid size at baseline and post-treatment was 34.23 ± 9.66 mm and 27.18 ± 9.39 mm respectively (p-value <0.0001). The mean change in fibroid size in women with vitamin D deficiency following vitamin D supplementation was 6.79 ± 1.98 mm. In a study conducted by Munusamy et al., 2017 they have reported 78% prevalence of uterine fibroids in Pakistani women.[9] Lastly, a study found that the mean change in size of fibroids over 6 months with and without vitamin D supplementation was 7.14 S.D 3.86 and -0.28 S.D 1.98, showing that vitamin D did indeed decrease uterine size whereas non supplementation lead to an increase in size of the fibroid.[10]

A similar study was conducted by Paffoni et al.[12], who visited two infertility clinics in Italy with 126 fibroid women and 256 controls. They discovered that the mean serum concentration of vitamin D was 18.0 ± 7.7 ng/mL in fibroid women than in controls as 20.8 ± 11.1 ng/mL. The author found that 37% of patients had adequate vitamin D levels, compared to 45% of controls, while 15% of women with fibroid had significant deficiencies.[12]

In another cross-sectional investigation, Sabry et al.[13] recruited 50 controls who did not have fibroid and 104 women who did. The study was carried out in Egypt. The mean serum vitamin D3 concentrations in fibroid cases were 19.7 ± 11.8 ng/mL and 22.3 ± 6.5 ng/mL in controls. According to a retrospective examination of the data, women with adequate vitamin D3 had an estimated 32% reduced incidence of fibroids than those with vitamin D insufficiency [Baird and colleagues].[14]

Similar results have also been reported by Ajmani et al.[15] in 2018 (42.7% vs. 20.0%; p<0.001; 95%CI OR=13.9) in India. Compared to controls, women with uterine fibroids had a significantly reduced mean serum concentration of vitamin D3 (10.81±6.18 vs. 22.91±16.18, p<0.0001), according to Singh et al. (2018).[16] In Oskovi et al. study, the mean vitamin D levels in patients were 6.54±4.66 ng/ml and 8.18±5.16 ng/ml in controls, with a p-value of 0.009.[17]

According to Alsharif et al.'s meta-analysis, vitamin D supplementation is an affordable and non-invasive therapeutic option that can replace surgery.[5] According to Ciebiera et al., low 25-hydroxyvitamin D levels have been linked to uterine fibroids symptoms. Ciebiera M. and colleagues came to the conclusion in a study that paricalcitol supplementation might be a viable noninvasive medical treatment for uterine fibroids.[18] Dalla-Valasa and colleagues came to the conclusion that 1,25-dihydroxyvitamin D influences apoptosis, modifies a number of genes related to cell growth, encourages cell division, and increases the production of proteins.[8]

Additionally, a meta-analysis by Mohammadi et al. confirmed that blood vitamin D levels and the

presence of uterine fibroids were inversely related across various groups, with the effect being most noticeable in Asian cohorts.[19] Similarly, Okoro et al. discovered that women with uterine fibroids had far lower vitamin D levels than healthy controls, highlighting the fact that vitamin D insufficiency is a risk factor that may be changed.[6]

According to Suneja et al., vitamin D3 administration can help with menorrhagia, pelvic discomfort, and dysmenorrhea, among other fibroids-related symptoms. The clinical alleviation and blood vitamin D elevation were in line with our findings, even though the leiomyoma volume reduction was rather slight.[20]

Vitamin D serve as a therapeutic alternative to safely inhibit UL growth, as evidenced by Corachan et al. in a xenograft animal model.[21] In a case-control study including 90 women, the mean concentration of 25-(OH)D3 was significantly lower in women with UL compared to the controls. As the levels of 25-(OH) D3 decreased in the subsequent trial, the UL size rose correspondingly (p=0.014).[22] There was no correlation between vitamin D levels and the size or volume of UL; however, in a separate investigation with 124 women, the mean level of 25-(OH)D3 was significantly lower in women with UL.[23]

A study[24] showed that the presence of asymptomatic UFs was independently correlated with vitamin D deficiency, indicating that vitamin D level could be taken into account as a UF risk factor. Furthermore, it was found that these women had significantly higher rates and volumes of UF than the control group. Furthermore, a dose-dependent correlation was seen between the size of the fibroid tumor and the serum level of vitamin D. It is commonly known that vitamin D is the main factor regulating calcium homeostasis. 1, 25-dihydroxyvitamin D is an efficient anticancer medication that inhibits the growth of uterine cancer, according to numerous research. These findings and observations offer more proof in support of the potential application of 1, 25(OH)2D3 or its potent analogs for nonsurgical treatment of uterine leiomyoma.[24]

Conclusion

This study found that in women who are vitamin deficient, vitamin D supplementation decreases the size of the fibroid. Therefore, in order to reduce surgical intervention for symptomatic fibroids and prevent needless surgery, we advise women with uterine fibroids to regularly take vitamin D supplements.

Ethical Approval: The IRB/EC approved this study via letter no. CPSP/REU/OBG-2019-059-9801 dated March 03, 2023.

Conflict of Interest: None

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Authors' Contribution

SR: Conception.

UA: Design of the work.

SH: Data acquisition, analysis, or interpretation.

UA, SH: Draft the work.

SR: Review critically for important intellectual content.

All authors approve the version to be published.

All authors agree to be accountable for all aspects of the work.

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