

## Original Article

## Role of Vitamin D supplementation on the size of Uterine Leiomyomas in Women with Vitamin D Deficiency

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### Abstract

**Objective:** To determine the role of vitamin D supplementation on size of uterine leiomyomas in vitamin D deficient woman.

**Methods:** The study was conducted in the Department of Obstetrics and Gynaecology, Rawalpindi, from July 2019 to January 2020. This was a quasi-experimental study. A probability consecutive sampling method was used. Sixty-five women with a diagnosis of 1 to 2 uterine leiomyomas measuring 4–8 cm in diameter, vitamin D insufficiency and experiencing heavy vaginal bleeding were included. The 25-hydroxyvitamin D levels in the blood were checked. Vitamin D was then administered in five dosages over a period of ten weeks, with each patient receiving a total dose of 50,000 IU of vitamin D after every fourteen days. After 6 months, an ultrasound was done to determine the size of the fibroid. The mean size of leiomyomas was compared before and after vitamin D for six months using a paired t-test.

**Results:** Mean age of the patients was  $35.85 \pm 6.140$  year. Mean age at menarche of the patients was  $11.62 \pm 1.206$  year. Mean marital life of the patients was  $9.47 \pm 6.046$  year. Mean Hb levels of the patients were  $11.406 \pm 1.1875$  mg/dl. Mean size of leiomyoma before treatment was  $54.170 \pm 4.5493$  mm, while mean size of leiomyoma after treatment was  $44.991 \pm 2.7046$  mm, with a p-value of 0.001.

**Conclusion:** Vitamin D supplementation has been demonstrated to considerably reduce the growth of uterine fibroids. It would seem that females with vitamin D insufficiency can effectively treat their uterine fibroids by taking vitamin D supplements.

**Keywords:** Vitamin D Deficiency, Uterine Fibroids, Leiomyoma Size.

### Introduction

The leiomyomas are the most frequent solid benign gynaecological uterine tumours. They developed from the clonal growth of a single myometrium cell<sup>1</sup>. It is the most frequent benign pelvic tumour in women of childbearing age, with incidences ranging from 5.4% to 77% globally<sup>2</sup>.

Particularly when they are located in the submucosa, UFs are frequently linked to severe morbidity. Anaemia, severe and protracted menstrual bleeding, pelvic pain, and infertility are all possible symptoms for women with UFs.<sup>3</sup>

Uterine fibroid is a multifactorial disease. Uterine fibroids are largely fueled by ovarian hormones, including estrogen and progesterone, growth factors, cytokines, and chemokines. Smooth muscle cells that have a large amount of the extracellular matrix (ECM), which is made up of proteoglycans, fibronectin, and collagen, are what make up fibroids. The chance of developing uterine fibroids is influenced by genetic and epigenetic variables, even though the origin of uterine fibroids is unclear. Other risk factors have also been found like age, race and ethnicity, family history, body mass index, early exposure to pollutants from the environment, vitamin D insufficiency, and other factors are some of these.<sup>4,5</sup>

Depending on the location and size of the fibroids, UFs can present with a variety of symptoms and degrees of severity. Since UFs are thought to affect up to 70% of women at some point in their lives, physicians must pay close attention to how they affect society and women's quality of life<sup>6</sup>. Depending on the symptoms, age, general health, concern for fertility preservation, and individual patient's preferences, management options for uterine fibroids include medicinal therapy, radiologically guided procedures, and surgical interventions. To treat UFs, non-surgical procedures and therapies should be taken into consideration<sup>7</sup>.

Approximately 70% of women of reproductive age have leiomyomas, which are more common in young age.<sup>8</sup>

There are no minimally invasive procedures which can successfully shrink leiomyoma size without side effects. The pathophysiology of uterine leiomyomas is unclear. Vitamin D deficiency has a higher chance for development of uterine fibroids.

Since the majority of women with uterine leiomyoma have low vitamin D levels ( $\leq 20$  ng/mL), normal vitamin D levels may be linked to a lower risk of uterine fibroids.<sup>9</sup>

Additionally, the serum level of 25-hydroxyvitamin D3 is significantly lower in affected women than in control women, indicating an inverse relationship between total leiomyoma volume and vitamin D serum levels.<sup>10</sup>

#### Contributions:

SA, SY - Conception, Design  
KM, SY - Acquisition, Analysis,  
Interpretation  
SA, SY - Drafting  
MS, S - Critical Review

All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

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These findings suggest that vitamin D may be important for the growth of leiomyomas. The vitamin D, or more specifically, its active metabolite 1,25[OH]2D<sub>3</sub>, is important for calcium and phosphate regulation in the body.

Since vitamin D has been shown to have antiproliferative properties and antitumorigenic agent in cancer cells. It affects proliferation, cell cycle progression, the Wnt/-catenin pathway, and apoptosis has therefore been shown to be a key mechanism by which vitamin D exerts its anticancer effects.<sup>11,12</sup>

According to a cross-sectional study done in Iran, women with uterine leiomyomas had mean blood levels of 25-hydroxyvitamin D3 that were lower ( $21.37 \pm 7.4$  ng/mL) than women without uterine leiomyomas ( $24.62 \pm 9.21$  ng/mL).<sup>13</sup> Another cross-sectional observational study found an inverse correlation between serum 25-hydroxyvitamin D levels and the volume of uterine leiomyomas ( $p=0.000$ ) and concluded that participants with big fibroid masses had significantly lower blood 25-hydroxyvitamin D levels than those with smaller fibroid masses.<sup>14</sup>

The size of the leiomyoma was significantly reduced in females treated with vitamin D compared to placebo (52.58 versus 61.11 mm, respectively) in a double-blinded, prospective randomised trial in which females diagnosed with uterine leiomyoma and vitamin D deficiency were treated with vitamin D or placebo every two weeks for 10 weeks. These findings suggested that vitamin D3 supplementation can be a useful medical therapy for the management of uterine leiomyoma by reducing the mass of the tumour.<sup>15</sup> The goal of this study was to determine how vitamin D supplementation affected the size of uterine leiomyomas in women who were vitamin D deficient. By reducing the size of the uterine leiomyoma and subsequently its symptoms without necessitating any significant surgical procedures, this study will contribute to lowering the burden of disease on healthcare providers and enhancing the wellness of women.

## Materials And Methods

The study was conducted in the Department of Obstetrics and Gynaecology from July 2019 to January 2020. It was a quasi-experimental study, and non-probability consecutive sampling technique was used for collection of samples. With a 95% confidence interval and 80% power of the study, a sample size of 65 women was estimated.

The women of reproductive age with a diagnosis of 1 to 2 uterine leiomyomas measuring 4–8 cm in diameter, vitamin D insufficiency and experiencing heavy vaginal bleeding were included.

The women with co-morbid disorders such as hypertension (BP140/90mmHg), diabetes (BSR>200mg/dl), heart disease (abnormal ECG and medical record), hepatic (ALT or AST>40IU, hepatitis B or C), or renal diseases (creatinine>1.5mg/dl), those who are pregnant, going through menopause, and already taking vitamin D supplements, were excluded.

The informed consent was taken from women included in the study after approval from the hospital's Ethical Board of RMU. A thorough history of demographic information was gathered, such as heavy monthly flow, anaemia, dysmenorrhea, pelvic pressure, backache, bloating, frequent urination, and dyspareunia. The levels of serum 25-hydroxyvitamin D were determined and recorded on a Performa with particular design features. The Vit D was then administered in five doses over ten weeks, with each patient receiving a total dose of 50,000 IU of vitamin D after every fourteen days. The size of the uterine leiomyoma was recorded six months after the start of the treatment by trans-abdominal ultrasound by gynecologist. The level of vitamin D was also measured after 6 months.

The data was entered using SPSS version 25, and the outcomes were assessed. While qualitative factors like the presence of heavy menstrual bleeding, anemia, dysmenorrhea, pelvic pressure, backache, bloating, frequent urination, and dyspareunia were expressed as the frequency of occurrence and the percentage of women who experienced these symptoms, quantitative factors like age, the size of the uterine leiomyoma, and serum levels of 25-hydroxyvitamin D3 were expressed as the mean value along with the standard deviation. The mean size of the leiomyoma before and after receiving vitamin D treatment for six months was compared using a paired t-test. P-values of 0.05 or lower were considered to represent statistically significant relationships.

## Results

For this study, a total of 65 women with uterine fibroids and vitamin D insufficiency were chosen. The patients' mean age was  $35.85 \pm 6.140$  years. The patients' mean age at menarche was  $11.62 \pm 1.206$  years. In the age range of 31 to 45, the patients' average length of marriage was  $9.47 \pm 6.046$  years. The patients' mean haemoglobin levels were  $11.406 \pm 1.1875$  mg/dl.

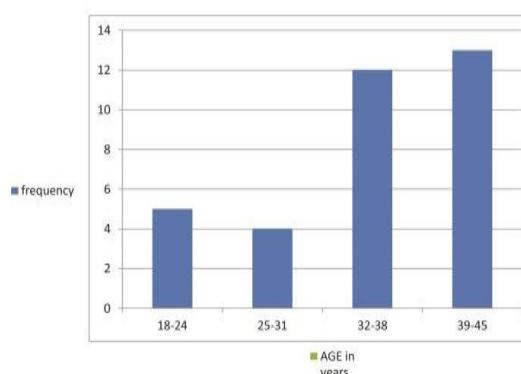
**Table 1: Change in size of leiomyoma before and after the treatment with vitamin D**

	<b>n</b>	<b>Mean</b>	<b>Std. Deviation</b>	<b>p-value</b>
<b>Size of leiomyoma (mm) before treatment</b>		54.170	4.5493	
<b>Size of leiomyoma (mm) after treatment</b>	65	44.991	2.7046	0.001

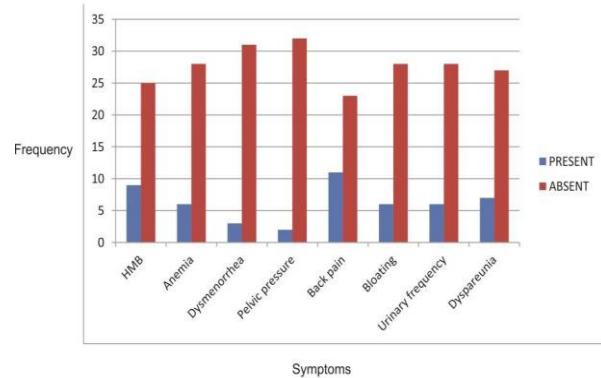
According to the patients' age distribution, 42 patients (64.4%) were above 30 years, and 23 patients (35.3%) were between the ages of 18 and 30. Six patients (9.2%) suffered dysmenorrhea, while 11 patients (16.9%) had anaemia. 3 individuals (4.6%) had pelvic pressure. Back pain affected 22 (33.8%) people. 12.4% of the patients had bloating. 5.6% of the patients experienced frequent urination. Six (9.2%) of the patients suffered dyspareunia.

**Table 2: Change in levels of vitamin D before and after the treatment with vitamin D**

	n	Mean	Std. Deviation	p-value
<b>Level of vit. D (ng/ml) before treatment</b>		<b>16.613</b>	<b>1.3728</b>	
<b>Level of vit. D (ng/ml) after treatment</b>	<b>65</b>	<b>36.050</b>	<b>1.5268</b>	<b>0.001</b>

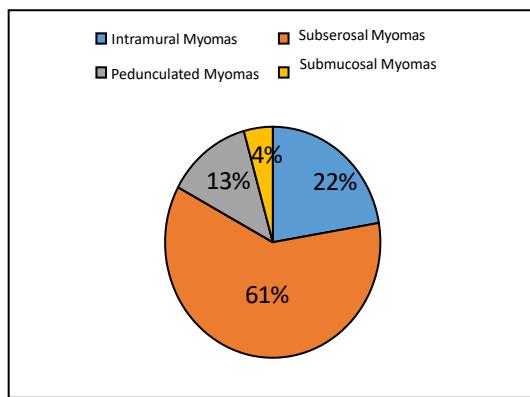


**Figure 1: Graphical representation of the frequency distribution of the age group**

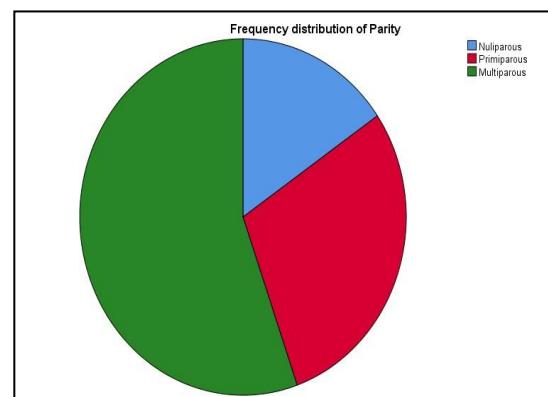


**Figure 2: Graphical representation of the frequency distribution of symptoms**

According to location of leiomyoma distribution, 14(21.9%) had intramural myomas, 40(61.5%) had subserosal myomas, 9(13.8%) had pedunculated myomas and 3(4.3%) had submucosal myomas (Figure 3). According to parity distribution, 10(15.3%) were nulliparous, 19(29.2%) were primiparous and 36(55.3%) were multiparous (Figure 4). Mean size of leiomyoma before treatment was  $54.170 \pm 4.5493$  mm, while mean size of leiomyoma after treatment was  $44.991 \pm 2.7046$  mm with p-value of 0.001 (Table 1), which is statistically significant. A paired t-test was applied. The mean level of vitamin D before treatment was  $16.613 \pm 1.3728$  ng/ml, while the mean level of vitamin D after treatment was  $36.050 \pm 1.5268$  ng/ml, with a p-value of 0.001 (Table 2), which is statistically significant. A paired t-test was applied.



**Figure 3. Percentage distribution of the location of Leiomyoma**



**Figure 4: Frequency distribution of parity**

## Discussion

The aim of this study was to investigate the effect of vitamin D supplementation on the development of uterine leiomyomas. Our study showed that women with vitamin D deficiency develop leiomyomas that are considerably smaller when they take a vitamin D supplement. Additionally, following the administration of vitamin D, the levels of 25-hydroxyvitamin D3 increased significantly. A class of steroid substances known as vitamin D has a profound effect on a variety of bodily functions, including the neurological, immunological, and genitourinary systems. There are different types of vitamin D, including vitamin D1 (calciferol), which is most frequently found in fish oils, vitamin D2 (ergocalciferol), which is found in plants, and vitamin D3 (cholecalciferol), which is made by the skin. The liver's 25-hydroxylase enzyme transforms vitamin D into 25-hydroxyvitamin D [25(OH)D], which is

then hydroxylated in the kidneys to form 1,25-dihydroxyvitamin D [1,25(OH)D]. 1,25(OH)D, the most active form of this vitamin, has activity in nearly all human body tissues.<sup>16</sup>

UFs are exceedingly frequent benign uterine tumours that can seriously harm a patient's physical and mental health. Fibroids with symptoms are often handled and treated. However, there is currently no evidence to recommend routine therapy for the majority of asymptomatic UFs. Therefore, it is crucial to estimate the risk of new fibroid formation and give effective therapy. It is well accepted that age and vitamin D status have a substantial impact on UFs. It is yet uncertain, though, what clinical level of vitamin D is necessary for new fibroid development. In the current investigation, we discovered that vitamin D levels may help assess the likelihood that asymptomatic UFs will develop.<sup>5</sup>

Meta-analysis by Alsharif et al. concluded that vitamin D supplementation is a cost-effective and non-invasive therapeutic alternative to surgery<sup>9</sup>. Low 25-hydroxyvitamin D levels have been associated with symptoms of uterine fibroids, according to Ciebiera et al. In a study, Ciebiera M and associates concluded that paricalcitol supplementation would be a possibility for a noninvasive medical treatment for uterine fibroids.<sup>17</sup>

Our conclusion that treatment with 1,25-dihydroxyvitamin D3 reduces the growth of uterine leiomyoma tumours, matched with the results of a study by El Sabeh M11. Dalla-Valasa & associates concluded that 1,25-dihydroxyvitamin D affects apoptosis, alters several genes linked to cell development, promotes cell proliferation, and stimulates protein synthesis. These characteristics form the basis for 1, 25-dihydroxyvitamin D3's ability to combat leiomyoma tumours.<sup>12</sup>

Furthermore, meta-analysis by Mohammadi et al. Confirmed an inverse relationship between serum vitamin D levels and the presence of uterine fibroids among different populations, particularly in Asian cohorts, where the effect was most pronounced (SMD = -1.20; p < 0.001)<sup>18</sup>. Similarly, Okoro et al. Found significantly lower vitamin D levels in women with uterine fibroids compared to healthy controls, emphasising that vitamin D deficiency is a modifiable risk factor.<sup>10</sup>

Suneja et al. highlighted the effect of vitamin D3 supplementation in improving the associated symptoms of fibroids, including menorrhagia, pelvic pain, and dysmenorrhea. While the leiomyoma volume reduction was modest, the symptomatic relief and serum vitamin D elevation were consistent with our outcomes.<sup>19</sup>

## Conclusions

To conclude, we demonstrated that vitamin D deficiency was independently related to the presence of asymptomatic UFs, suggesting that vitamin D level might be considered in a UF risk measure. In addition, it was discovered that the frequency and volume of UF were considerably greater in these women as compared to the control participants; this finding is in keeping with previous publications and indicates a negative link between blood Vitamin D levels and the prevalence and volume of UF. In addition, there was a dose-dependent relationship between the amount of vitamin D in the serum and the size of the fibroid tumour. Vitamin D is well recognised as the primary regulator of calcium homeostasis. Numerous studies have shown that 1, 25-dihydroxyvitamin D is an effective anticancer drug that suppresses the growth of uterine cancer. These observations and results provide additional evidence in favour of the possible use of 1, 25(OH)2D3 or its powerful analogues for nonsurgical uterine leiomyoma therapy. It has been demonstrated that vitamin D Supplementation can shrink uterine fibroids. It would seem that using vitamin D supplements could be an efficient medical care for uterine fibroids.

## Author Information

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