



## Original Research Article

## Does vitamin D play a role in uterine fibroids? A case control study

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## ABSTRACT

**Introduction:** Uterine fibroids are monoclonal tumors of uterine smooth muscle cells. They are found in 20-40% of females in the reproductive age group. Ovarian hormones play an important role in its etiology. Recent studies have shown that low serum 25(OH) vitamin D levels are associated with increased risk of uterine fibroids.

**Aim :** To investigate the association between serum vitamin D levels and uterine fibroids.

**Materials and Methods :** A case control study was conducted in a tertiary care hospital among 183 women between the age of 18-50 years with uterine fibroids who attended obstetrics and gynecology department and 183 women of the same age group who had no uterine fibroids attending comprehensive health checkup clinic. Serum 25(OH) vitamin D levels were estimated in both groups by electrochemiluminescence immunoassay.

**Results:** Statistical analysis was performed using IBM SPSS version 20.0. P value of <0.05 was considered statistically significant. The mean serum 25(OH) vitamin D levels of women with uterine fibroids were  $15.03 \pm 6.996$  ng/mL and  $16.629 \pm 8.020$  ng/mL in women without uterine fibroids. There was no statistically significant difference in serum 25(OH) vitamin D levels between women with and without uterine fibroids (P=0.132).

**Conclusion:** Serum 25(OH) vitamin D levels were found to be deficient in both groups irrespective of the presence or absence of uterine fibroids. Hence, it can be concluded that the study conducted in 366 women could not find a direct association between low serum 25(OH) vitamin D levels and uterine fibroids.

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## 1. Introduction

Uterine fibroids are slow growing benign neoplasms of uterus. They are also known as fibromyomas, leiomyomas or simply myomas. Based on their number, size and location, they can cause menstrual irregularities, either spasmodic or congestive dysmenorrhoea, infertility, recurrent abortions, abdominal pain, fullness in the

abdomen, pressure symptoms on nearby viscera like urinary bladder, ureter and rectum and pregnancy complications.<sup>1</sup> Uterine fibroids can become large and cause marked disfigurement of the uterine cavity and its surface which interferes with implantation.

Uterine fibroids are seen in 20-40% of females in the reproductive age group.<sup>2</sup> It is most likely diagnosed during their forties.<sup>3</sup> It invokes a heavy burden on the health of women and health care framework. Ovarian hormones play a vital role in its etiology.<sup>4</sup> Obesity, low parity, early age of

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menarche, black population, positive family history, genetic factor, diet, stress, and sedentary lifestyle have effects on growth and development of uterine fibroids.<sup>5-7</sup>

Latest research works have shown that low serum vitamin D levels take part an imminent contribution in the occurrence of uterine fibroids.<sup>8,9</sup> Vitamin D receptor (VDR) is a nuclear receptor which brings about biological actions of vitamin D.<sup>10</sup> Recent study has shown that VDR is present in myometrium as well as endometrium of uterus.<sup>8</sup> Calcitriol modulates gene expression by binding to VDR and later to vitamin D response elements which are situated on target genes (proximal promoter areas, distal enhancers, introns and intergenic regions) and it regulates the gene expression which can cause arrest of cell growth, differentiation and also programmed cell death.<sup>11</sup> Loss or inadequate VDR expression could be a causative element for development of uterine fibroids.<sup>12</sup> This shows that loss of functions of vitamin D because of either decreased levels of serum vitamin D or decreased VDR expression can be a risk for uterine fibroid growth.

Few studies showed no association between low levels of vitamin D and uterine fibroids. Our research work was aimed to investigate the association between serum 25(OH) vitamin D levels and uterine fibroids as there is a controversy and also, presently Indian studies are sparse in this regard.

## 2. Materials and Methods

Case control study was carried out in a tertiary care hospital.

### 2.1. Inclusion criteria

183 women between 18-50 years of age attending obstetrics and gynecology Department as cases and 183 age matched women without uterine fibroids attending comprehensive health check up as controls.

### 2.2. Exclusion criteria

Women with age group below 18 years and above 50 years of age, diabetes mellitus, hypertension, renal disease, liver disease, gastrointestinal problems, malnutrition, skeletal disease, and any chronic illness, pregnancy, lactation, menopause, women on hormonal treatment for past 3 months, women on vitamin D and calcium supplementation.

### 2.3. Study procedure

Institutional ethics committee clearance was taken. Informed written consent was taken from the participants. A detailed history of the patients was taken on the first outpatient department visit. Diagnosis was based on patient's history, complete physical examination including pelvic examination. An ultrasound scan was done to confirm the presence or absence of uterine fibroids.

### 2.4. Serum 25 (OH) vitamin D Estimation

2mL blood was drawn by venipuncture and serum was separated by centrifuging at 3000 rpm (revolutions per minute) for 5 min. Serum was stored at -20°C until the estimation of 25(OH) vitamin D was done. 25(OH) vitamin D was measured from the serum using electro chemiluminescent immunoassay (ECLIA). The equipment and reagent used was Cobas E411 and vitamin D total Roche reagent [Roche Diagnostics India Pvt. Ltd. Andheri (East) Mumbai – 400069]. Subjects were classified as vitamin D deficient, insufficient, and sufficient based on the serum vitamin D concentration of < 20, 20-30 and >30 ng/mL respectively.<sup>13</sup>

## 3. Results

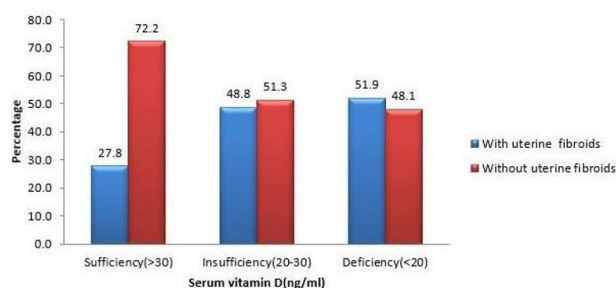
Statistical analysis was carried out applying IBM SPSS version 20.0. Categorical variables were indicated using frequency and percentage. Numerical variables were indicated by mean and standard deviation (SD). To test the statistical significance of categorical factors between with and without uterine fibroids, Chi square test was done. Student's "t" test was used to test the statistical significance of the difference in the mean of age and body mass index (BMI) between with and without uterine fibroids, and Mann-Whitney U test was used for serum vitamin D level. P value of less than 0.05 was regarded statistically significant.

There were 183 subjects each in both the groups. Mean  $\pm$  SD was found out for age, BMI, and 25(OH) vitamin D levels [Table 1]. 25(OH) vitamin D level was analyzed in both groups. Of the total study subjects (366), 268 women was vitamin D deficient, 80 were vitamin D insufficient and 18 was vitamin D sufficient. 139(51.9%) women who had deficient vitamin D levels developed uterine fibroids; 39(48.8%) women having insufficient vitamin D levels developed uterine fibroids and 5(27.8%) women having sufficient vitamin D levels developed uterine fibroids [Figure 1]. The results showed statistically no significant association between low serum vitamin D levels and uterine fibroids.

**Table 1:** Mean  $\pm$  SD of age, BMI & 25(OH) vitamin D levels in women with and without uterine fibroids

|                             | Age<br>(yrs)         | BMI<br>(kg/m <sup>2</sup> ) | 25 (OH)<br>vitamin D<br>(ng/mL) |
|-----------------------------|----------------------|-----------------------------|---------------------------------|
| With uterine<br>fibroids    | 42.54 $\pm$<br>6.235 | 25.983 $\pm$<br>4.233       | 15.03 $\pm$<br>6.996            |
| Without uterine<br>fibroids | 35.16 $\pm$<br>9.348 | 23.588 $\pm$<br>4.209       | 16.629 $\pm$<br>8.020           |
| P value                     | <0.001               | <0.001                      | 0.132                           |

P<0.05-statistically significant



**Fig. 1:** Association between serum 25(OH) Vitamin D levels and uterine fibroids.

#### 4. Discussion

In our study, we noticed that serum vitamin D levels were decreased in most of the women with and without uterine fibroids.

Some of the studies have shown correlation between low serum vitamin D levels and uterine fibroids. Case control study done by Paffoni et al (2013) in Italy among 384 women (128 cases and 256 controls) of reproductive age group revealed that serum 25(OH) vitamin D<sub>3</sub> was remarkably decreased in women with uterine fibroids in comparison to controls.<sup>14</sup> A cross-sectional study carried out by Sabry et al (2013) in Egypt in 154 premenopausal women (104 cases and 50 controls) showed that serum 25-hydroxy vitamin D<sub>3</sub> was markedly reduced in women with uterine fibroids than controls.<sup>8</sup> Using particulars from the National Institute of Environmental Health Sciences (NIEHS) uterine fibroid study conducted in Washington, DC, Baird et al. (2013) retrospectively analyzed the levels of serum vitamin D in 1036 women (620 blacks and 416 whites) and he found a decrease in serum 25(OH) vitamin D levels concluding that vitamin D is inversely correlated with the development of uterine fibroids.<sup>9</sup> Ciebia et al (2016) investigated the outcome of low levels of vitamin D on the risk of developing uterine fibroids. They reported that low serum vitamin D level is a risk factor for uterine fibroids.<sup>5</sup> Oskovi Kaplan et al (2018) did an observational cross-sectional study in 68 premenopausal women with uterine fibroids and 56 healthy women in Turkish population. This study revealed that vitamin D level was noticeably reduced in study group with respect to control group.<sup>15</sup> Singh et al (2019) conducted an observational study in Jamshedpur in 72 women aged 20\_50 years with uterine fibroids and 72 age-matched healthy controls. It revealed an absolute indirect association of vitamin D deficiency and uterine fibroids in eastern Indian population.<sup>16</sup> The authors have suggested for further studies with larger population. Mohammed et al (2020) did a meta analysis in 1730 subjects (835 cases and 895 controls) showed that serum vitamin D level was greatly decreased in women with uterine fibroids in stipulated populations.<sup>17</sup> Ajmani et al (2018) observed a

similar association between vitamin D and uterine fibroids and they went on to propose cohort and interventional studies to establish a causal link between uterine fibroids and decreased vitamin D levels.<sup>18</sup> Srivastava et al (2020) did a cross-sectional study in Lucknow in 90 women (45 cases and controls) and finalized that Vitamin D<sub>3</sub> deficiency is crucially related to the development of uterine fibroids.<sup>19</sup> A cross-sectional study was carried out by Choudhary S et al (2021) in 140 women [equal number of cases and controls] in Delhi which showed a reciprocal relation between uterine fibroids and vitamin D levels. The authors have recommended larger prospective longitudinal studies so as to have more number of participants as well as to get rid of the confounding factors that might affect the development of uterine fibroids.<sup>20</sup>

Unlike the observations in above studies, there was no definite association between deficient vitamin D levels and risk of female reproductive tumors in a meta-analysis done by Yan et al (2018) among 8189 participants (2391 cases and 5798 controls). Similar inference was made out in women with reproductive benign tumors. Nevertheless, deficient vitamin D level can be a risk factor for women with malignant reproductive neoplasm. Apart from this, occurrence of vitamin D deficiency was more in women with uterine fibroids. [52.36%] and the control groups [48.70%]. The authors have commented that vitamin D deficiency would be an insignificant controller of incidence of fibroids and its development.<sup>21</sup> Susanna D et al. (2015) did a cross sectional evaluation of serum vitamin D levels among self reported uterine fibroid diagnosed in 3590 US women aged 20-54 years, reporting no association between serum vitamin D levels and adjusted odds of uterine fibroids in the whole population. They observed that uterine fibroids in white women are associated with low levels of vitamin D levels but not in black women.<sup>22</sup>

The low serum vitamin D levels in participants of both the groups in our study may denote the underlying vitamin D deficiency in Indian population as documented in earlier research works.<sup>23,24</sup> The prevalence of vitamin-D deficiency is 70-100% in the common public all over India.<sup>25</sup> Considering the widespread occurrence of vitamin-D deficiency in our country, females are mostly affected.<sup>16</sup>

The lifestyle of Indian people like covered clothing pattern, use of umbrella, sunscreens and other cosmetics to prevent sunlight exposure, vegetarian food along with the low socioeconomic status have a salient contribution in causing low serum vitamin D levels. Apart from that, majority of Indians are not aware of the requirement of intake of additional Vitamin D as supplement form. The high cost of the same also contributes to the reduced consumption of vitamin D supplements. Another reason for lower level of vitamin D is the darker skins which is commonly seen among Indians that synthesizes a considerably lower amount of vitamin D in contrast to light

skinned people like Caucasians.<sup>25</sup> Majority of our subjects in both the groups were homemakers, doing indoor job and therefore not exposed adequately to sunlight and therefore might have led to low levels of serum vitamin D. Distinct latitude and ethnicity might have an impact on the occurrence of uterine fibroids.<sup>19</sup>

In our control group, majority of the women did not develop uterine fibroids even though their serum vitamin D levels were low. There is a considerable variation in mean age among both the groups:  $42.54 \pm 6.235$  years in cases and  $35.16 \pm 9.348$  years in controls ( $P < 0.001$ ). Thus, implying a younger age among majority of the subjects in the control group. Majority of them had a normal BMI as well ( $25.983 \pm 4.233 \text{ kg/m}^2$  in cases and  $23.588 \pm 4.209 \text{ kg/m}^2$  in controls;  $P < 0.001$ ). These might have not led to the development of uterine fibroids in controls. We could not obtain a direct association between serum vitamin D levels and uterine fibroids.

Our data suggest the disease susceptibility and severity is not dependant lonely on low serum vitamin D levels. Low serum vitamin D level along with some other related factors might have led to uterine fibroids. In our study, mean age of women with uterine fibroids was  $42.54 \pm 6.235$  years and mean BMI was  $25.983 \pm 4.233 \text{ kg/m}^2$  ( $P < 0.001$ ) which would have aided in developing uterine fibroids.

Previous study by Paffoni et al showed the correlation of vitamin-D deficiency related to the number of uterine fibroids and not to the dimensions.<sup>14</sup> Thus, indicating that vitamin-D deficiency take part in the development of uterine fibroids rather than on its growth. For verifying the underlying reason for the same, the authors have suggested for cohort studies and interventional studies too. Nevertheless, Sabry et al noted an inverse correlation between low serum vitamin D<sub>3</sub> level and uterine fibroids.<sup>8</sup> They concluded that subjects with larger volumes of uterine fibroid were having lower serum vitamin D level and conversely also. Study by Singh et al did not show considerable association between the number of fibroids and size with serum vitamin D levels, thus indirectly indicating its role in growth and development of uterine fibroids.<sup>16</sup> Therefore, the exact contribution of vitamin D in uterine fibroids is obscure.

A prospective long lasting cohort study with a larger sample size is strongly recommended with consecutive evaluation of vitamin D status. Several other causative factors for uterine fibroids such as age, elevated BMI, diet, ovarian hormones, early age of menarche, low parity, family history, stress, genetic, environmental and metabolic factors has to be taken in account to find out a definite reason for uterine fibroids.

## 5. Limitations

The sample size was smaller. The half-life of 25(OH) vitamin D in blood is only about 15 days. A one-time

measurement of Vitamin D would not refer to the lifetime status. Vitamin D deficiency persisting for a long duration might lead to the development and/or growth of uterine fibroids. Several other causative factors for uterine fibroids such as age, elevated BMI, diet, ovarian hormones, early age of menarche, low parity, family history, genetic element, metabolic factors, stress and climate related factors has to be taken in account to find out a definite reason for uterine fibroids.

## 6. Conclusion

Serum 25(OH) vitamin D level was deficient in women with uterine fibroids and women without uterine fibroids.

In order to authenticate a definite association between low serum vitamin D levels and uterine fibroids, we need to point out women with low serum vitamin D levels and monitor them periodically to know whether they would literally get uterine fibroids. A prospective long lasting cohort study with a larger sample size, taking in account of other causative factors is strongly recommended.

## 7. Conflict of Interest

None.

## 8. Source of Funding

None.

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