



## Relation between Vitamin D and Uterine Fibroid

Aml A. Hammad <sup>a\*</sup>, Shereen B. Elbohoty <sup>a</sup>, Sahar M. Hazzaa <sup>b</sup>,  
Medhat S. Hewedy <sup>a</sup> and Mohamed N. El-Gharib <sup>a</sup>

<sup>a</sup> Obstetrics and Gynecology Department, Faculty of Medicine, Tanta University, Egypt.

<sup>b</sup> Clinical Pathology Department, Faculty of Medicine, Tanta University, Egypt.

### Authors' contributions

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## ABSTRACT

**Background:** Uterine fibroids (UFs) are the most common benign tumors affecting women of reproductive age]. patients with uterine fibriod suffer from pelvic pain, menorrhagia, dysmenorrhea/dyspareunia, pressure-related symptoms, miscarriage, and subfertility. The aim of this study was to assess the relationship between occurrence, size, and clinical symptoms of uterine fibroid and the serum level of Vitamin D.

**Methods:** The study was designed as an observational case control study.

This study was conducted at Tanta University Maternity Hospital at the department of obstetric and Gynecology from March 2020 to September 2020. This study was conducted on 75 women in their reproductive age (20-45 yrs) recruited at Tanta obstetric and gynecology department (inpatient wards), they were subdivided into two groups: Group A: case group: 50 Women with uterine fibroid. Group B: control group: 25 Women with normal uterine examination and transvaginal ultrasound. Measuring the level of serum vitamin D3 in both control and women with uterine fibroid.

**Results:** The age, in case group, ranged from 20-45 yrs with mean level 30.50± 4.56 yrs and in control group ranged from 20-45 with mean value 31.01+ 5.11 yrs. the diagnostic performance of vitamin D test in diagnosing uterine fibroid through illustrating sensitivity and specificity of vitamin D level to predict uterine fibroid. Area under the curve was 0.881 with cut off value 14.3 ng/ml, the sensitivity of vitamin D to predict the fibroid was 79.3%, the specificity was 66.7 and test accuracy was 74.4%.

\*Corresponding author

**Conclusions:** The current study showed a significant association between vitamin D3 deficiency in reproductive age women and the occurrence of uterine fibroid, the mean vitamin D3 level in the case group was 13.8±7.93 ng/ml and in the control group was 20.79±8.95 ng/ml.

- There is correlation between vitamin D3 level and the size of uterine fibroid.
- Vitamin D3 deficiency is widely spread among the study population with 80 % prevalence while vitamin D3 insufficiency is prevalent in 14% among study participants

*Keywords: Vitamin D; uterine; fibroid.*

## 1. INTRODUCTION

“Uterine fibroids (UFs) are the most common benign tumors affecting women of reproductive age” [1]. “patients with uterine fibroid suffer from pelvic pain, menorrhagia, dysmenorrhea/dyspareunia, pressure-related symptoms, miscarriage, and subfertility”[2]. “Currently, there is no effective medicinal treatment for UFs, There are a range of current management options: removal of the uterus (hysterectomy), removal of the fibroid lesions (myomectomy), uterine artery embolization, image-guided focused ultrasound thermal therapy, and, in mild cases, reassurance and observation” [3]. “Currently, novel noninvasive treatment options for UFs – such as localized gene therapy” [4], “oral green tea extracts, and selective progesterone receptor modulators”[5].

“Vitamin D (Vit D) is a prohormone produced in the skin via a sunlight-initiated reaction and metabolically converted to the active metabolite 1,25-dihydroxyvitamin D3 [1,25(OH)2D3], mainly in the liver and kidneys”[6].

“Vit D exerts its effects via activation of its cellular receptor (vitamin D receptor [VDR]), which in turn alters the transcription rates of target genes responsible for various biological responses. Local production of 1, 25(OH) 2D3 is dependent on circulating precursor levels, which may explain the association of serum Vit D deficiency with various diseases. Diverse functions for Vit D have been confirmed by the presence of VDR in a wide range of human tissues, including skin, colon, brain, pancreas, and breast, as well as activated T and B lymphocytes, monocytes, and macrophages”[7].

Feng has demonstrated “VDR expression in both the myometrium and the endometrium of the human uterus, throughout the menstrual cycle, in addition to UF tissues” [8].

“The ability of 1,25(OH)2D3 to inhibit growth and promote differentiation of a variety of cell types

has suggested diverse functions in preventing cancers, modulating the immune system, and controlling various endocrine systems”[3].

Sharon has also demonstrated that “Vit D is an antifibrotic factor that inhibits the growth of human fibroid cells in a dose-dependent fashion by significantly reducing many of the transforming growth factor beta 3 (TGF-β3)–mediated effects such as the TGF-β3 induction of fibronectin and collagen type 1 protein expression, the induction of protein expression of plasminogen activator inhibitor-1, Furthermore, they have demonstrated the ability of Vit D to safely shrink UF lesions in rats” [9].

These findings suggest that “Vit D may be a potentially useful therapeutic agent for the nonsurgical management of UFs” [3].

This report evaluates “the possible correlation between serum Vit D3 levels and the tumor burden of UF disease in a diverse population of women of reproductive age” [10].

The aim of this study was to assess the relationship between occurrence, size, and clinical symptoms of uterine fibroid and the serum level of Vitamin D .

## 2. PATIENTS AND METHODS

The study was designed as an observational case control study.

### 2.1 Study Setting

This study was conducted at Tanta University Maternity Hospital at the department of obstetric and Gynecology from March 2020 to September 2020.

### 2.2 Study Population

This study was conducted on 75 women in their reproductive age (20-45 yrs) recruited at Tanta obstetric and gynecology department (inpatient wards), they were subdivided into two groups:

Group A: case group: 50 Women with uterine fibroid.

Group B: control group: 25 Women with normal uterine examination and transvaginal ultrasound.

### 2.3 Inclusion Criteria

Age: Women in reproductive age 20 - 45 yrs.

At least one uterine fibroid with a diameter less than 5 cm (Small), equal or more than 5cm (Large) detected by transvaginal or abdominal ultrasound to be considered as case group women.

Normal uterine examination and transvaginal ultrasound to be considered as control group women.

### 2.4 Exclusion Criteria

- Adenomyosis and endometriosis.
- Pregnancy.
- Lactation.
- Abortion and pregnancy loss in the last 6 months.
- Vitamin D replacement.
- Ovarian cyst of any size or nature.
- Hormonal contraception.
- Malignancy.
- Chronic kidney and liver disease.

### 2.5 Sample Size Justification

The required sample size has been calculated using STATA program version 10, setting alpha error at 5 % and power at 80%

## 3. METHODOLOGY

All patients in the two groups were subjected to:

**Consent:** An informed oral medical consent was taken for all enrolled women in both groups after full explanation of the steps and significance of this study.

**History taking:** A complete history was taken including:

Personal and demographic data (Age, residence, social status and habits). Degree of sun exposure:

By asking women about the number of hours per day of direct sun exposure. Categories were < 1

hour/day for low exposure, 1 hour/day for medium exposure and more than 1 hour/day for high sun exposure. Menstrual history (Duration, frequency, regularity and menstrual pain (dysmenorrhea)).

- Patient complaint (Asymptomatic, uterine bleeding, Pain, voiding disorder, infertility).
- Medical, surgical and drug history.

**Physical examination:** General, abdominal, pelvic and vaginal examination.

Body Mass Index (BMI) weight in kilograms divided by the square of height in meters. Categories were (According to the WHO, BMI is classified as underweight < 18.5, normal (18.5-25), overweight (25-30) obese class (1) (30-35), obese class (2) (35-40).

**Investigation:** Laboratory Investigations:

- CBC (Complete Blood Count).
- Serum vitamin D level.

### 3.1 Technique of Serum Vitamin D Measurement

**Specimen collection and handling:** 4 ml venous Blood sample was collected by venipuncture. 2 ml was put on EDTA tube for CBC and 2 ml was kept in standard sampling tube without anticoagulants, clotting was allowed. Then, the blood sample was centrifugated at a speed of 4000 rpm. This results in separation of the plasma from other blood components. Vitamin D level in the sample was analyzed using automated Electrochemilumescence Immuno assay ECLIA (Cobas\_e\_ immunoanalyser), the used Kit was manufactured by Roche, Germany (Fig. 1).

**Ultrasound examination:** Ultrasound evaluation was performed by transvaginal ultrasound (TVU) for all enrolled subjects, while transabdominal ultrasonography was performed as needed for some subjects for whom TVU was not sufficient to evaluate the fibroid lesions particularly, large fundal fibroids or virgin women.

**The following parameters were evaluated by Pelvic US:** Total uterine size, as measured in three perpendicular planes. Number of fibroid lesions. Size of fibroid lesions (small= less than 5 cm. equal or large than 5 cm).

Position/location of each fibroid lesion within the uterus (uterine fundus, lower uterine segment,

cervix, extrauterine). Unusual characteristics (echogenicity, presence of calcifications, presence of central necrosis, etc) of each fibroid lesion. Sonographic appearance of leiomyomas was defined as symmetrical, well defined, hypoechoic and heterogenous masses. Myoma less than 5cm was considered small while if myoma was equal or more than 5cm, it was considered large.

### 3.2 Study Outcomes

#### 3.2.1 Primary outcome

Measuring the level of serum vitamin D3 in both control and women with uterine fibroid.

#### 3.2.2 Secondary outcome

Study the correlation between serum vitamin D3 level and uterine fibroid and its size (Small less than 5 cm, Large equals or more than 5cm).

## 4. RESULTS

This study was carried out at Tanta University Hospital at the department of Obstetrics and

Gynecology. A total of 75 women in reproductive age group were recruited in this study. Women were divided into two groups, Case group, including 50 women with uterine leiomyoma and Control group Including 25 women with normal uterine examination and ultrasound.

The age, in case group, ranged from 20-45 yrs with mean level  $30.50 \pm 4.56$  yrs and in control group ranged from 20-45 with mean value  $31.01 \pm 5.11$  yrs.

BMI in the case group, ranged from 18-35 kg/m<sup>2</sup> with in value  $30.23 \pm 2.23$  and in control group ranged from 18-35g/m<sup>2</sup> with mean value  $28.13 \pm 2.63$ kg. There was no statistical difference between case and control groups regarding age and BMI (P > 0.05).

Hb level in the case group ranged from 8.3-13.24 gm/dl mean value  $11.8 \pm 1.56$  and in control group ranged from 11.00-13.7 gm/dl with mean value  $12.3 \pm 1.85$ . The mean Hb level in the cases group was lower than the control group but there was no statistically significant difference between the two groups (P = 0.005).

**Table 1. Comparison between case and control groups regarding age and BMI**

	Groups		X-test P value
	Group A	Group B	
Age / years			
Range	20.00 - 45.00	20.00 - 45.00	0.856
Mean	$30.50 \pm 4.56$	$31.01 \pm 5.11$	
SD			
BMI kg/m <sup>2</sup>			
Range	18.00-35.00	18.00-35.00	0.064
Mean	$30.23 \pm 2.23$	$28.13 \pm 2.63$	
SD			

**Table 2. Comparison between both groups regarding the hemoglobin (Hb)**

hemoglobin (Hb) Level gm/dl	Groups		t-test P value
	Group A	Group B	
Range			
Mean	8.3-13.24	11.00-13.7	0.005
SD	$11.8 \pm 1.56$	$12.3 \pm 1.85$	

**Table 3. Comparison between case and control groups regarding vitamin D<sub>3</sub>**

Vitamin D3 level (ng/ml)	Groups		Test P value
	Group A	Group B	
Range			
Mean	2.80-32.50	3.60-36.76	0.001*
SD	$13.80 \pm 7.63$	$20.79 \pm 8.90$	

Vitamin D3 level in the case group ranged from 2.80- 32.50 ng/ml with mean value 13.80±7.63 ng/ml and in control ip ranged from 3.60-36.76 ng/ml with mean value 20.79 ±8.90 ng/ml. The level of vitamin D was significantly less in cases than in controls with (P value 0.001) thus there was a statistically significant difference between case and control groups regarding vitamin D level (P < 0.05).

On using the Endocrine Society Practice Guidelines criteria of vitamin D status, in the case group, out of 50 cases 40 women (80%) were found deficient. vitamin D level less than 20 ng/ml while in controls they were 2 women (8%) with odds ratio, 7 women in the case group (14%) were vitamin D level, while in controls they were 3 women (12%) with odds ratio.

Shows the characteristics of uterine fibroid in the case group regarding (size, location and the presenting symptom). As regard the size of uterine fibroid, small fibroid < 5 cm large fibroids > or = 5cm. The number of women having fibroid size more than 5cm was 19 females (38%) lesser than the number of women having fibroid size <5cm di was 31 females (62%).

As regard the different locations of uterine fibroid, the subserous fibroid was the highest in number 30 women (60%) followed by intramural fibroid in 14 women (28%), submucos fibroid in 6 women (12%).

In the case group, women who were exposed to sunlight less than 1 hr were 60% while 26% and 14% of women in the same study group were exposed to daily sunlight for 1 hr or more than one hour respectively.

On the other hand, only 40% of women in the control group were exposed to daily sunlight for less than 1 hr while most of the control group 44% were exposed for more than 1 hr and 16 % of women were exposed to sunlight for around one hour on daily basis. There was highly statistical significant difference.

Vitamin D3 level in cases UF less than 5cm was 5.7-36.3 with mean value 12.24±4.34 .while in cases with UF more than 5cm was 3.6-31.1 with mean value 10.66±5.55 (P value 0.47) thus there was no statistically significant difference between case and control groups regarding vitamin D level (P < 0.05).

**Table 4. Comparison between case and control groups regarding the status of vitamin D level**

Vitamin D level	Groups				P value	Chi square
	Group A		Group B			
	No	%	No	%		
Deficient	40	80.0%	2	8%	0.001	26.690
Insufficient	7	14%	3	12%		
Sufficient	3	6%	20	80%		
Total	50	100.0%	25	100.0%		

*P is significant if ≤ 0.05 \*significant*

**Table 5. Number, type, size and location of the fibroids of the group A (n= 50)**

	no	%
number		
1-2	44	88%
multiple	6	12%
type		
Subserous	30	60%
Intramural	14	28%
submucos	6	12%
Site of intramural type:		
Ant	7	50%
post	3	21.4%
Ant&post	4	28.6%
size of myomas		
<5cm	31	62%
>5cm	19	38%

**Table 6. Comparison between case and control groups regarding the duration of daily sunlight exposure**

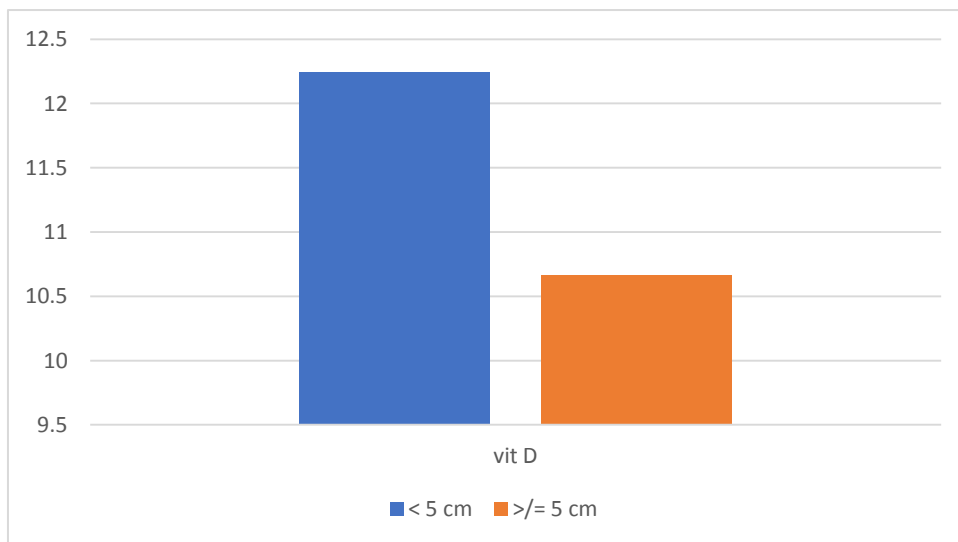
Duration of Sun Exposure/day	Groups				P value
	Group A		Group B		
	No	%	No	%	
<1 hr	30	60%	10	40%	0.0001*
1 hr	13	26%	4	16%	
>1 hr	7	14%	11	44%	
Total	50	100.0%	25	100.0%	

*P is significant if ≤ 0.05 \*significant*

**Table 7. Relation between serum vitamin D<sub>3</sub> level and the of fibroid in the case group**

Vitamin D3 level (ng/ml)	Size of fibroid		P value
	< 5 cm	≥ 5 cm	
Range			
Mean	5.7-36.3	3.6-31.1	0.47
SD	12.24± 4.34	10.66±5.55	

*Significant if ≤ 0.05 N.S. Not significant*

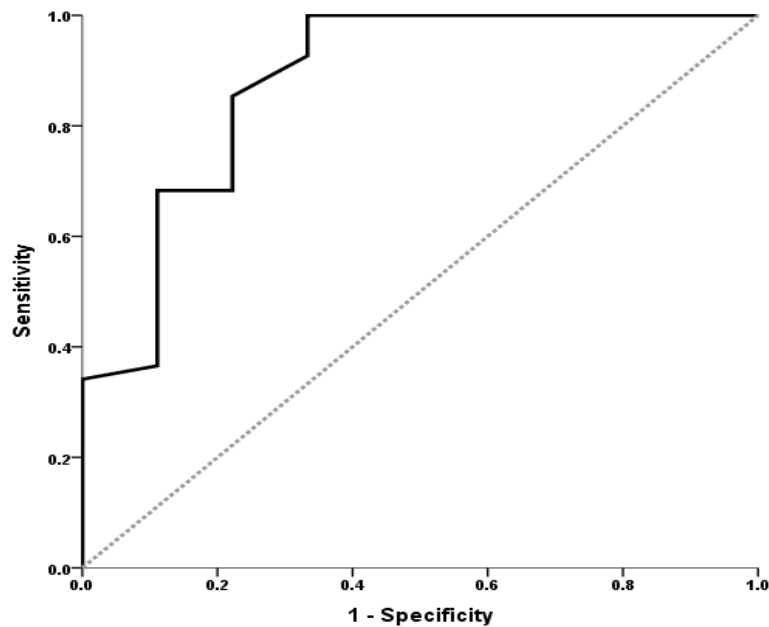


**Fig. 1. Relation between Vit D level and size of myoma**

**Table 8. Shows the diagnostic performance of vitamin D test in diagnosing uterine fibroid through illustrating sensitivity and specificity of vitamin D level to predict uterine fibroid**

<b>AUC</b>	<b>0.881</b>
95% CI	0.737-1
p	<0.001
Cut off	14.3
Sensitivity (%)	79.3
Specificity (%)	66.7
PPV (%)	93.2
NPV (%)	100
Accuracy (%)	74.4

*ROC, receiver operating characteristic curve; AUC, area under ROC curve; PPV, positive predictive value; NPV, negative predictive value*



**Fig. 2. ROC curve to predict the cut off value of vitamin D to uterine fibroid**

Shows the diagnostic performance of vitamin D test in diagnosing uterine fibroid through illustrating sensitivity and specificity of vitamin D level to predict uterine fibroid. Area under the curve was 0.881 with cut off value 14.3 ng/ml, the sensitivity of vitamin D to predict the fibroid was 79.3%, the specificity was 66.7 and test accuracy was 74.4%.

## 5. DISCUSSION

“Uterine fibroids are benign growths that develop from the muscle tissue of the uterus. 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”[11].

“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”[12].

“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”[13].

The sources of vitamin D mainly comes from ultraviolet B ray via the skin (80%) and the remaining 20% from the diet [14].

There is a positive relationship between vitamin D deficiency and uterine fibroids. Among the Turkish, African and American population, there is a positive uterine leiomyoma and vitamin D relationship [15]. Furthermore, calcitriol treatment of human uterine fibroid tissue may reduce the cell proliferation, and thereby inhibit molecular pathways for fibrosis [12].

The aim of work of the current study was to study the relation between vitamin D and uterine fibroid to elucidate this aim total of 75 women in reproductive age group were recruited in this study. Women were divided into two groups, Case group, including 50 women with uterine leiomyoma and Control group Including 25 women with normal uterine examination and transvaginal ultrasound

In the current study, there was no significant difference between the cases and control group as regard to age which was the same results in the study done by Hajhashemi et al. [16] who studied 69 patients with uterine leiomyomas who had vit D deficiency [109].

Ciavattini and others. who studied 208 women diagnosed with uterine fibroids and concomitant hypovitaminosis D found no significant difference in between cases and control group regarding to age .

In the present study half of the studied cases were house wife and the other half were worker while in the study done by Chowdhury et al. [13] who studied a total of 47 participants diagnosed as uterine fibroids (size less than 5 cm) to see the effect of vitamin d supplementation on the size of uterine fibroids they found that majority of the participants were housewives (70.3%).

Thomas and his colleges. [17] examined determinants of low levels of 25(OH)D3 concentrations among older, predominantly white, hospitalized patients and found that vitamin D intake, winter season, and being housebound were independent predictors of vitamin D deficiency.

In this study, there was no significant difference in between smoking and fibroid in case group which disagrees with the study done by Haq et al. [18] .

As regard to number of fibroids, in the current study there was 88 % (44 cases) of the studied cases had 1-2 fibroid but 12% (6 cases) had multiple fibroids, which agrees with the study done by Ciavattini et al. [19] who studied “208 women diagnosed with uterine fibroids and concomitant hypovitaminosis D found that 125 patients (60.1%) presented a single fibroid, while multiple fibroids were detected in 83 patients (39.9%)”.

In our study, the mean Vitamin D3 level in the patient group was 13.80 ng/ml while in the control group was 20.79 ng/ml with high significant value in between (P= 0.001) which in agreement with the study done by Ajmani and others. [20] who studied 75 patients with fibroid and 75 as a control to examine the vit D effect on fibroids found that The mean vitamin D level 12.58±4.09 ng/ml and 18.99±5.72 ng/ml for cases and control respectively with a significant difference in between (p=0.001)

Also, Sabry and others., 2013 study the role of vitamin D on fibroid found that the mean level of serum 25-OH Vitamin 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). Therefore, it can be considered that

vitamin D deficiency is a possible risk factor for the occurrence of UFs

Oskovi Kaplan and his colleoges., [15] reported similar results in a control study conducted on 124 premenopausal women presented with fibroid and 68 control women) to correlate the role of vitamin D levels in uterine fibroids. The mean vitamin D levels of the case group was significantly lower than control group (6.54 ± 4.66 ng/mL vs. 18.18 ± 5.16 ng/mL, respectively p=0.009).

Ciavattini and his colleoges.[19] studied 208 women diagnosed with uterine fibroids and concomitant hypovitaminosis D also stated that, a significant difference in the mean 25-OH-D3 serum level between the women in patient group and the women in the control group (20.4±5.9 vs 39.0±8.0 ng/mL; P < 0.001)

On the contrary, to our result Yan et al. [21] made a meta-analysis to study the occurrence of vitamin D deficiency in the case and control groups in 8 studies indicated that there was no significant correlation between low vitamin D levels and the odds of various benign and malignant gynecological tumors

“In the present study, 80% of the studied patients group had deficient vit D while 14 % were insufficient and only 6% were sufficient . The increasing trend of vitamin D deficiency in recent years could be due to several factors, such as lifestyle changes, being an indoor worker, urbanization, environmental pollution, and decreased outdoor activity” [22]. “Furthermore, low levels of physical activity correspond with an increasing risk of obesity, and obesity can directly increase the odds of UL through increased estrogen production by adipose tissue” [23].

In this study, lower serum Vitamin D levels (deficient and insufficient) are inversely correlated with UFs in the cases with P=0.001 which agrees with the study done by Paffoni, et al. [24] who showed similar findings in 2013, where 128 women with UFs and 256 controls were chosen. Women who had the UFs were diagnosed by transvaginal ultrasound and were selected if the fibroid had a mean diameter ≥ 10 mm. Women with UFs had significantly lower vitamin D levels than the controls, and the percentage of women with vitamin D deficiency was significantly higher in the group with UFs when compared to the control



In contrast to our results, Mitro *and others*. [25] performed a retrospective cross-sectional study on 3590 subjects and did not find correlation between 25(OH)D levels and uterine leiomyomas; they reported that vitamin D deficiency increase the risk of leiomyoma in white women but not in black women. Although the study recruited a large number of women with uterine leiomyoma, few distinct points from the current study - are found. First, the retrospective nature of the study. Second, the study included both premenopausal and postmenopausal women. Third, the study depended on subjects' statement using a question if she had or ever been told to have uterine fibroid without objective diagnosis by ultrasound [25].

Furthermore, several studies have been performed on the relation between vitamin D deficiency and uterine fibroids. Among the Turkish population, in the study done by Oskovi Kaplan et al. [15] their study conducted on 124 premenopausal women presented with fibroid and 68 control women) to correlate the role of vitamin D levels in uterine fibroids, there is a positive uterine leiomyoma and vitamin D relationship. In African American populations, in the study done by Baird et al. [26] there is a positive correlation between vitamin D deficiency and presence of uterine fibroids.

Li et al. [27] also stated that patients with vitamin D deficiency had increased risks of UFs.

For most people, the major source of vitamin D is skin production by exposure to sunlight [28]. As regard to duration of daily sunlight exposure and uterine fibroids there was a significant difference in between cases and control group with  $P=0.0001$  which mean increased duration of daily sunlight exposure leads to decreased incidence of uterine fibroid that coincide with the study done by Baird, et al. [29] who studied a randomly selected 35- to 49-year-old women who were members of an urban health plan during 1996–1999. Fibroid status was determined by ultrasound screening of premenopausal women (620 blacks, 416 whites) they found that women with sufficient levels of vitamin D and had a sun exposure of more than one hour per day were less likely to get UFs. Sufficient vitamin D levels meant 32% less chance of having UFs, after controlling for other cofounders [30,31]

Currently, high-risk patients, those with positive history of UFs, Afro-Americans and those with elevated BMI, should be screened and offered supplementation, if necessary [23]. According to Ali and his colleagues. [32] women who would benefit from this management include also these with early menarche, nulliparous, and aged

As regard to relation between serum vitamin D<sub>3</sub> level and the size of fibroid, the mean serum vitamin D level in patients with fibroid size less than 5 cm was 12.24 ng/ml, while women with fibroid size equal or more than 5 cm had mean serum vitamin D level of 10.66 ng/ml with ( $P=0.47$ ) with no statistical significant difference between the size of fibroid and vitamin D which in line with the study done by Kumari et al. [33] who stated that there was a negative correlation between serum vitamin D levels and uterine fibroid size and number.

In line to our study, A recently published randomised clinical trial by Arjeh and others., [34] found that "vitamin D consumption did not significantly decrease the volume of fibroids in experimental group compared with control group".

Halder and his colleague., [35] stated that 1,25-dihydroxyvitamin D reduced ECM-associated protein expression in immortalized human uterine fibroid cells.

In 2012, Halder et al. [36] found that vitamin D treatment significantly decreased the size of UFs in the Eker rat animal model through the suppression of cell proliferation. They showed that estrogen and progesterone receptor on rat uterine leiomyoma cells reduced by receiving the 0.5-microgram per Kg of 1, 25-dihydroxyvitamin D<sub>3</sub>.

Halder and others., [37] have recently shown that uterine fibroids express lower levels of vit D receptor (VDR) compared with myometrium

Moreover, in 2018, Elhusseini et al. [38] found that low serum levels of vitamin D in mice were associated with an increased expression of sex steroid receptors in the myometrium and an increased expression of proliferation, fibrosis, and inflammation-related genes. In this study, the authors also presented that vitamin D deficient diet-enhanced DNA damage in the myometrium which may increase the risk of fibroid development later in life

Heaney and others., [39] also stated that Vitamin D3 also significantly reduced the expression levels of cell cycle regulatory proteins, such as CDK1, CDK2 and CDK4, in fibroid tumors

These data are of particular clinical relevance, since vitamin D could be a potential safe, nonsurgical therapy for the treatment of uterine fibroids [10].

Due to rare side effects and relatively high safety of vitamin D, combination therapies-drugs with additional simultaneous vitamin D supplementation could be also considered. According to a very recent study by Ali et al. [40] ulipristal acetate (UPA) and vitamin D share synergistic anti-fibroid activities. In this study, the combined therapy of UPA and vitamin D resulted in a significant inhibition of UF cell growth (lowest proliferation rate from all studied groups). This research is a milestone and can bring entirely new perspectives on how to treat UF.

As regard to the diagnostic performance of vitamin D test in diagnosing uterine fibroid, the sensitivity of vitamin D to predict the fibroid was 79.3%, the specificity was 66.7 and test accuracy was 74.4% with  $P < 0.001$ .

## 6. CONCLUSIONS

The current study showed a significant association between vitamin D3 deficiency in reproductive age women and the occurrence of uterine fibroid, the mean vitamin D3 level in the case group was  $13.8 \pm 7.93$  ng/ml and in the control group was  $20.79 \pm 8.95$  ng/ml.

- There is correlation between vitamin D3 level and the size of uterine fibroid.
- Vitamin D3 deficiency is widely spread among the study population with 80 % prevalence while vitamin D3 insufficiency is prevalent in 14% among study participants

## CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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