Serum Vitamin D_3 Levels in Women with and without Uterine Fibroids

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ABSTRACT:

BACKGROUND:

Uterine leiomyomas are the most common benign tumours of the female genital tract. They are a major source of morbidity for women and a frequent indication of gynecological surgery. Understanding the etiology of uterine fibroids remains incomplete. Vitamin D may be an unrecognized risk factor for their development.

OBJECTIVE:

To assess serum vitamin D_3 levels in women with and without uterine fibroids and to identify whether serum vitamin D_3 levels correlate with the severity of uterine fibroids disease.

METHODS:

This prospective case- control study involved 150 women in their premenopausal state who presented at the outpatient gynecology clinic at AL-Yarmook Teaching Hospital, Baghdad-Iraq. They were arranged into two groups; the control group consisted of 75 healthy women without uterine fibroids confirmed by ultrasound examination. The remaining 75 women, had at least one fibroid lesion of $2cm^3$ in volume or larger confirmed by transvaginal/ transabdominal ultrasound examination, represented the study group. All women enrolled in the study had similar demographic background. For each case woman, total uterine volume, and total volume of all existing fibroids were measured. Serum vitamin D_3 levels were measured for all participants by ELISA method. Statistical analysis was performed to compare serum vitamin D_3 levels across groups of women with and without uterine fibroids and to assess the correlation of serum vitamin D_3 levels with uterine fibroids burden.

RESULTS:

Serum vitamin D_3 levels were significantly (p=0.0001) lower among women with uterine fibroids compared to the control group with a mean value (15.81±8.64) ng/ml in women with uterine fibroid and (34.25±8.07) ng/ml in the control group. A significant negative correlation was found between serum vitamin D_3 levels and the increase in number of uterine fibroids (r=-0.623, p=0.0001) and the increase in total uterine fibroids volume (r=-0.742, p=0.0001).

CONCLUSION:

According to the present study, lower serum vitamin D_3 levels are significantly associated with the occurrence of uterine fibroids and serum vitamin D_3 levels inversely correlate with both uterine fibroids number and total uterine fibroids volume.

KEY WORDS: vitamin D deficiency, premenopause, uterine fibroids

INTRODUCTION:

Uterine fibroids (leiomyomata) are the commonest benign uterine tumours in women. Their lifetime prevalence is around 30%. The biology of fibroids is poorly understood and their cause remains unclear. They are often asymptomatic, but one in four women with fibroids are symptomatic [1,2].

They can present with a multitude of symptoms such as heavy menstrual bleeding, a feeling of pelvic pressure or pain, urinary or defecation problems. They may be associated with reproductive problems such as infertility and miscarriage [2-4].

At present, there is no effective medicinal treatment for uterine fibroids and research is still needed to determine the most appropriate treatment options for women with fibroids. Medical treatments are only

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used for short-term therapy. On the other hand, there is lack of evidence regarding the risks and benefits of long-term therapy and regarding the use of the newer medical agents [2,3].

Recent evidence from three independent research groups on populations from North Africa, east USA and central Europe have demonstrated an association between serum vitamin D deficiency and increased risk of uterine fibroids [5- 7]. It has been demonstrated that vitamin D is an antifibrotic factor that can inhibit the growth of human fibroid cells and that 1, 25-Dihydroxyvitamin D3 reduce TGF-beta3-induced fibrosis-related gene expression in human uterine fibroid cells [8]. Also it has recently been demonstrated that 1,25-dihydroxyvitamin D_3 inhibited the proliferation of human uterine leiomyoma cells in part by inhibitory catachol-O-methyltransferase, which is an estrogen metabolizing enzyme that is over expressed in human uterine leiomyomas [9]. Another animal study had demonstrated the ability of vitamin D to shrink uterine fibroids [10]. These findings can be useful in clinical practice through improving strategies for the management of this common disease. The aim of the present study was to investigate serum vitamin D_3 levels in women with and without uterine fibroids, and to identify whether its' levels correlate with the severity of uterine fibroids disease.

MATERIALS AND METHODS:

This study was a prospective case- control study conducted at Department of Obstetrics and Gynecology in cooperation with the Department of Radiology and Imaging at AL-Yarmouk Teaching Hospital in Baghdad, for a period of fourteen months extending from the first of January 2015 to the end of February 2016. All participants were recruited from the outpatient gynecology clinic. The study was approved by the Arab Board Committee for Medical Specialization. All women were informed about the nature of the study and only those who agree to participate were included. Verbal consent was obtained from all participants before enrolling them in the study.

A total of 150 premenopausal women were enrolled in the study They were divided into two groups; 75 women with a normal uterine structure, fibroid - free based on transvaginal ultrasound (control group) and 75 women with at least one fibroid lesion with a mean volume of $2cm^3$ or greater confirmed by transvaginal/ transabdominal ultrasound who were recruited from those presenting to the gynecology clinic with either asymptomatic fibroid or with various uterine fibroid related symptoms (study group).

For both groups, the inclusion criteria were women in their reproductive age; their age range was (18-50) years who were in the premenopausal status (menstrual cycle day 3 serum follicle-stimulating hormone <10 mIU/ml); the exclusion criteria were women with current pregnancy or a pregnancy within 6 months prior to the start of the study, currently lactating, or lactating within 6 months prior to enrollment, those with history of myomectomy or hysterectomy or who had experienced an abortion or miscarriage within 6 months prior to enrollment to the study. Also women who had a history of medical illness (liver, renal, malignancy, hypertension, diabetes mellitus, thyroid or parathyroid disease, multiple sclerosis, autoimmune disorders) or were currently using any hormonal treatment or a vitamin supplement or who had used any hormonal treatment or a vitamin supplement within the last 6 months prior to enrollment were also excluded from the study.

For each woman, a formal questionnaire was filled including her name, age, marital status, parity, the presenting complains in symptomatic woman and phone number. A careful history including past medical, surgical, gynecological, obstetrical history and family history were taken. History of drug use was also obtained. Physical and gynecological examination including pelvic and bimanual examination were done. Height was taken by scale meter and weight was measured then body mass index was calculated to all patients by dividing the weight of the participant in kilograms over the square of the height in meters.

Ultrasound evaluations were performed by transvaginal ultrasound (TVU) for all women , while transabdominal ultrasonography was performed as needed for some women in whom TVU was not sufficient to evaluate the entire fibroid lesions – particularly, large fundal fibroids. To prevent misdiagnoses, women were excluded if sonographic evaluation of the characteristics of the uterus was difficult or in the presence of suspected adenomyosis. The Ultrasonography assessment was performed

using SIEMENS ACUSON X300– fitted with a 6.5 MHz endovaginal probe for the transvaginal scan and a 2.5/3.5 MHz convex probe for the abdominal scan. The following parameters were evaluated by ultrasound: total uterine size measured in three perpendicular planes, volume of all fibroid lesions, number of fibroid lesions, position/location of each fibroid lesion within the uterus and unusual characteristics for each fibroid lesion like echogenicity, presence of calcifications or central necrosis, etc. The volume of the uterus and all fibroids were determined according to the prolate ellipsoid formula ($V= (a \times b \times c) \times 0.523$), where a is the height, b is width, and c is depth.

Blood samples were drawn from antecubital vein or from the dorsum of the hand of each woman with great care , two ml of collected blood was sent for FSH (menstrual cycle day 3) and another 2ml of blood was collected without using tourniquet for serum vitamin D_3 concentration measurement and samples were transferred into clean plane tube, left at room temperature for 30 minutes for clotting, centrifuged at 2,000 rpm for 10 minutes and the separated serum was transferred into tube and frozen at -20^0C until the time of analysis. All the specimens were clearly labeled with names of patients along with the date and the time of collection. Prior to use, all specimens were allowed to come to room temperature ($+22^o$ C to $+28^o$C) and mixed by gentle inversion. Grossly hemolyzed or lipemic serum samples were not used. The tests were done in hormonal and biochemistry laboratory at AL- Yarmook Teaching Hospital. Quantitative determination of Vitamin D_3 was done by enzyme linked immunosorbant assay (ELISA) using 25-OH vitamin D ELISA kit (EUROIMMUN Medizinische Labordiagnostika AG.D-23560 Luebeck, Germany). Vitamin D deficiency was diagnosed at level of <20 ng/mL.

Statistical analysis:

Analysis of data was carried out using the available statistical package of SPSS-22 (Statistical Packages for Social Sciences- version 22). Data were presented in simple measures of frequency, percentage, mean, standard, deviation, and range (minimum-maximum values). The significance difference of different means (quantitative data) was tested using Students-t-test for difference between two independent means, or ANOVA test for difference among more than two independent means. The significance difference of different percentages (qualitative data) was tested using Pearson Chi-square test (χ^2-test) with application of Yate's correction or Fisher Exact test whenever applicable. Pearson correlation was calculated for the correlation between two quantitative variables with its t-test for testing the significance of correlation. The correlation coefficient value (r) either positive (direct correlation) or negative (inverse correlation) with value <0.3 represent no correlation, 0.3-<0.5 represent weak correlation, 0.5-<0.7 moderate strength, >0.7 strong correlation. In addition to correlation the r^2 was calculated (The coefficient of determination), i.e. when value of r=0.58, then r^2=0.34, this means that 34% of the variation in the values of y may be accounted for by knowing values of x or vice versa. Statistical significance was considered whenever the P value was equal or less than 0.05. Receiver Operated Characteristic (ROC) curve was applied in order to determine the cut-off value for vitamin D_3 determination of uterine fibroid with regard to optimum sensitivity and specificity.

RESULTS:

The main characteristics of the included women are shown in Table 1. There was no statistically significant difference in age between the two study groups and the same was true for the parity and the BMI, with *p*-values of 0.489, 0.066 and 0.589 respectively.

Regarding Table 2, uterine volume was significantly (*p*-value =0.0001) higher in women with uterine fibroid compared with controls, as the mean value of uterine volume in the study group was (336.91±156.77) ranging from (75.31-897.47) while the mean value of uterine volume in the control group was (52.62±13.38) ranging from (30.64-108.55). Table 3 showed the numbers and total volume of uterine fibroids in the study group. Fifty-two percent of women had one uterine fibroid while 30.7% of women had two fibroids and 17.3% had three and more fibroids. For the total uterine fibroids volume, 54.7% had uterine fibroid volume <50 cm^3, 40% had uterine fibroid volume of 50-199 cm^3, and 5.3% had uterine fibroid volume≥200 cm^3 and the mean of the total uterine fibroid volume (cm^3) was 74.52±77.79. Interestingly, there was a statistically significant (p-value = 0.0001) lower

levels of vitamin D_3 among women with uterine fibroids compared with the controls, as mean value of serum vitamin D_3 in women with uterine fibroid was (15.81±8.64) ng/ml ranging from (2-36) while the mean value of serum vitamin D_3 in the control group was (34.25±8.07) ng/ml ranging from (14-52). The median of vitamin D_3 was 18ng/ml in the study group while the median of vitamin D_3 was 34ng/ml in the controls (Tables 4, 5 and Figure 1). Regarding Table 6, there was a significantly lower vitamin D_3 level as the number of uterine fibroids increased (p-value = 0.0001). The mean of serum vitamin D3 in women with one uterine fibroid was (20.56±6.87) ng/ml while the mean of serum vitamin D3 in women with three & more uterine fibroids was (6.92±6.36) ng/ml. Furthermore, lower serum vitamin D_3 levels were significantly associated with increased total uterine fibroids volume (p-value=0.0001). In other worlds, for women with uterine fibroids, the lower the serum vitamin D_3 levels, the larger the total uterine fibroids volume. The mean of serum vitamin D3 in women with uterine fibroid volume < 50cm^3 was (21.61±6.22) ng/ml while the mean of serum vitamin D3 in women with uterine fibroid volume => 200 cm^3 was (3.00±2.00) ng/ml. As shown in table 7, there is a weak negative correlation between serum vitamin D3 levels and age , BMI of women with uterine fibroid as (r =-0.390 , r= -0.456) respectively, and a moderate significant negative correlation with uterine volume(cm^3) in the study group as (r=-0.623); also table 7 and figure 2 show strong significant negative correlation between serum vitamin D_3 levels and total uterine fibroids volume, as r=-0.742. Figure 3 demonstrates Receiver operator curve (ROC), sensitivity and specificity of serum vitamin D_3 as a predictor of uterine fibroid. Regarding the cut off value of serum vitamin D_3, The result shows that if we use serum vitamin D_3 of 19.5ng/ml as a cut off value, it will give us sensitivity of (69.3%) and specificity of (94.7%) which is of low clinical value in diagnosing uterine fibroid and the same result obtained when we use serum vitamin D_3 of 21 ng/ml which will give us a little bit higher sensitivity (73.3) but lower specificity (93.3).

Table 1: Demographic characteristics of women with and without uterine fibroid.

		Uterine fibroid		Control		P value
		No	%	No	%	
Age (years)	20---24	3	4.0	8	10.7	0.489
	25---29	12	16.0	14	18.7	
	30---34	17	22.7	13	17.3	
	35---39	23	30.7	24	32.0	
	=>40	20	26.7	16	21.3	
	Mean±SD (Range)	35.2±6.6 (20-49)		33.7±6.8 (20-46)		
Parity	Primi	9	12.0	5	6.7	0.066
	Para 1	14	18.7	7	9.3	
	2	25	33.3	19	25.3	
	3	17	22.7	24	32.0	
	4 & more	10	13.3	20	26.7	
	Mean±SD (Range)	2.2±1.4 (0-6)		2.7±1.3 (0-6)		
BMI (Kg/m2)	Normal (18.5-24.9)	39	52.0	39	52.0	0.589
	Overweight (25-29.9)	35	46.7	33	44.0	
	Obese (=>30)	1	1.3	3	4.0	
	Mean±SD (Range)	24.8±2.1 (20.2-31.1)		25.2±2.4 (20.0-31.1)		
*Significant difference in proportions using Pearson Chi-square test at 0.05 level.						

Table 2: The uterine volume (cm^3) in women with and without uterine fibroids.

Uterine volume (cm3)	Uterine fibroid		Control		P value
	No	%	No	%	
<50	-	-	34	45.3	0.0001*
50---99	1	1.3	40	53.3	
100---149	5	6.7	1	1.3	
150---199	9	12.0	-	-	
200---249	9	12.0	-	-	
250---299	12	16.0	-	-	
=>300	39	52.0	-	-	
Mean±SD (Range)	336.91±156.77 (75.31-897.47)		52.62±13.38 (30.64-108.55)		
*Significant difference in proportions using Pearson Chi-square test at 0.05 level.					

Table 3: The numbers and total volume of uterine fibroids in the study group.

		Uterine fibroid	
		No	%
Uterine fibroid number	One	39	52.0
	Two	23	30.7
	Three &more	13	17.3
Total uterine fibroids volume (cm3)	<50	41	54.7
	50---99	11	14.7
	100---149	15	20.0
	150---199	4	5.3
	=>200	4	5.3
	Mean±SD (Range)	74.52±77.79 (3.48-388.11)	

Table 4: The percentage distribution and mean serum vitamin D_3 levels in women with and without uterine fibroids.

Serum Vit D3 (ng/ml)	Uterine fibroid		Control		P value
	No	%	No	%	
<10	18	24.0	-	-	0.0001*
10---19	34	45.3	4	5.3	
20---29	18	24.0	18	24.0	
30---39	5	6.7	35	46.7	
40---49	-	-	15	20.0	
=>50	-	-	3	4.0	
Mean±SD (Range)	15.81±8.64 (2-36)		34.25±8.07 (14-52)		
*Significant difference in proportions using Pearson Chi-square test at 0.05 level.					

Figure 1: The Box Plot distribution of vitamin D_3 (ng/ml) for women with uterine fibroid and the control group.

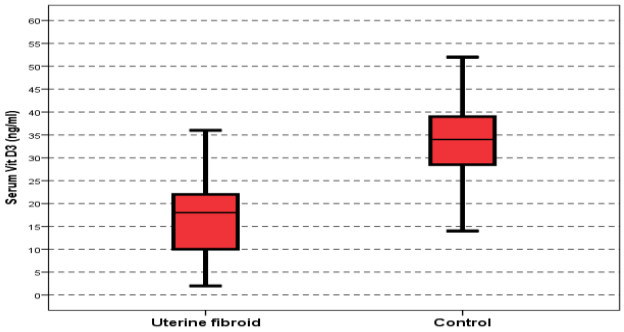

Table 5: The mean, median and range of serum vitamin D_3 in women with and without uterine fibroids.

	Uterine fibroid	Control
Count	75	75
Mean±SD	15.81±8.64	34.25±8.07
Standard Error of Mean	0.997	0.931
Range	2-36	14-52
Percentile 05^{th}	2	19
25^{th}	10	28
50^{th}(Median)	18	34
75^{th}	22	39
95^{th}	32	47
99^{th}	36	52
	P value	0.0001*
*Significant difference between two independent means using Students-t-test at 0.05 level		

Table 6: The different means of serum vitamin D_3 in the study group according to the number of fibroids and total uterine fibroids volume.

		Serum Vit D3 (ng/ml)	
		Uterine fibroid	
		No	Mean±SD
Uterine fibroid number	One	39	20.56±6.87
	Two	23	12.78±7.15
	Three & more	13	6.92±6.36
	P value		0.0001#
Total uterine fibroids volume (cm3)	<50	41	21.61±6.22
	50---99	11	12.91±5.61
	100---149	15	7.60±3.56
	150---199	4	8.00±5.42
	=>200	4	3.00±2.00
	P value		0.0001#
#Significant difference among independent means using ANOVA test at 0.05 level			

Table 7: The correlation of serum vitamin D3 with age, parity, BMI, uterine volume, total uterine fibroid volume in women with and without uterine fibroid.

		Serum Vit D3 (ng/ml)	
		Uterine fibroid	Controls
Age (years)	r	-0.390**	0.174
	P	0.001	0.136
Parity	r	-0.188	0.185
	P	0.106	0.112
BMI (Kg/m^2)	r	-0.456**	0.204
	P	0.0001	0.079
Uterine volume (cm^3)	r	-0.623**	-0.087
	P	0.0001	0.457
Total uterine fibroid volume (cm^3)	r	-0.742**	-
	P	0.0001	-
*. Correlation is significant at the 0.05 level.**. Correlation is significant at the 0.01 level.			

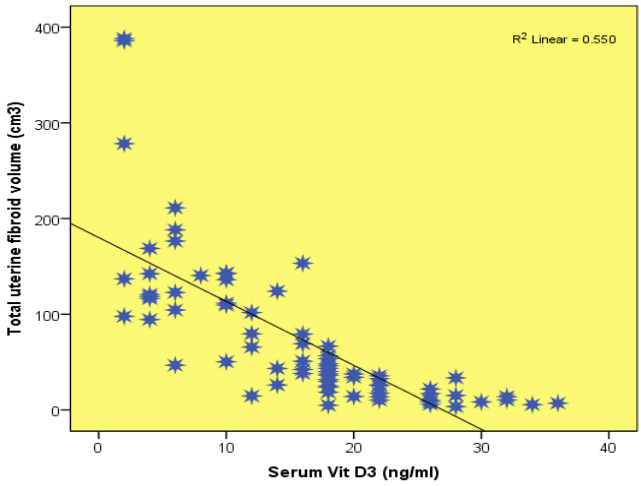

Figure 2: The correlation between TUF volume (cm3) and Vit D3 (ng/ml)

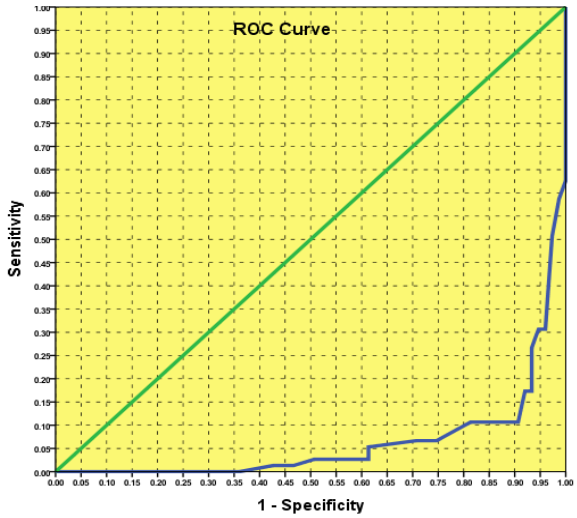

Figure 3: Receiver operator curve (ROC).

Area under the curve	Std. Error	P value	95% Confidence Interval	
			Lower Bound	Upper Bound
0.938	0.019	0.0001*	0.902	0.975
*Significant				

	Sensitivity%	Specificity%
Serum Vit D3 (ng/ml) Positive if Greater Than or Equal To; 13.0	37.3	100
15.0	41.3	98.7
17.0	49.3	97.3
18.5	69.3	96.0
19.5	69.3	94.7
21.0	73.3	93.3
23.5	82.7	93.3
25.5	82.7	92.0
26.5	89.3	90.7
27.5	89.3	81.3
28.5	93.3	74.7
29.5	93.3	70.7

DISCUSSION:

Identification of modifiable risk factors such as vitamin D deficiency could help in developing novel strategies for the prevention and/or treatment of uterine fibroids [5].

In this prospective case- control study, the possible correlation between serum vitamin D_3 and the occurrence and severity of uterine fibroids was investigated. Our results showed that serum vitamin D_3 was significantly lower in women with uterine fibroid compared to women without fibroids. Our findings were in agreement to those reported by Sabry et al. [5], Baird et al. [6], and Paffoni et al. [7], who documented lower levels of 25-hydroxyvitamin D_3 among cases compared to controls. Baird et al. reported that women with sufficient vitamin D levels had an estimated 32% lower odds of fibroids compared with those with vitamin D insufficiency.

In the current study, a strong significant inverse correlation was also found between serum vitamin D_3 levels and both uterine fibroids number and total uterine fibroids volume, in other words, lower serum levels of vitamin D_3, were associated with the largest uterine fibroid burden and vice versa. Our result agree with those reported by Sabry et al. [5] who found a significant negative correlation between serum vitamin D_3 levels and uterine fibroids burden, and partially agree with those reported by Paffoni et al. [7] who suggested that vitamin D had a role in the development rather than on the growth because deficiency tended to correlate with the number and not with the dimension of the lesions. In this study, a weak significant inverse correlation was found between serum vitamin D_3 levels and BMI in women with uterine fibroids. Wortsman et al .[11] and Datta et al.[12] had reported that obesity associated with the presence of vitamin D insufficiency was likely to be due to the decreased vitamin D_3 bioavailability from both cutaneous and dietary sources and that body fat may act as a reservoir for storing this fat-soluble vitamin. Also Marshall et al. [13] and Faerstein et al. [14] had reported that when BMI was adjusted for age, race, or ethnicity and compared, a BMI of ≥30.0 was associated with a 2.3-fold increase in the odds for having uterine fibroids. While Nesby-O'DellS et al. [15] reported that there is no correlation between vitamin D_3 levels and BMI, especially in black women.

In this study a weak significant inverse correlation was also found between serum vitamin D_3 levels and women's age. Heide Siggelkow [16] had reported that aging decreases the capacity of human skin to produce vitamin D_3. Aging also causes a decrease in calcium absorption and reduced production of the active form of vitamin D as a result of age-related decline in renal function[17]. William H. Parker [18] and Flake GP et al. [19] reported that a rapid increase of fibroid incidence after the age of 30 could be the result of age-related hormonal changes or an enhanced symptomatology from already existing fibroids. But Paffoni et al. [7] found that there was no association between 25-hydroxyvitaminD_3 deficiency and women's age.

Halder et al. [8] and Bläuer M et al. [20] had provided strong evidence for the biological role of vitamin D in the pathogenesis of uterine fibroids. They had demonstrated that vitamin D_3 is a potent antitumor agent that shrinks uterine fibroids in vitro. Also Al-Hendy and Badr [21] had suggested a dose-dependent inhibitory effect of vitamin D on human fibroid cell growth in vitro.

Also Halder SK et al. [22] had reported that vitamin D deficiency had been associated with higher expression for estrogen and progesterone receptors with enhanced estrogen and progesterone signaling in the myometrium. This may suggest that lifelong vitamin D deficiency status would be consistent with an earlier onset of uterine fibroids and a higher tumor burden.

Our data suggest that vitamin D_3 deficiency is a possible risk factor for the occurrence of uterine fibroids. However, further evidence is warranted to demonstrate a causal relationship. The most suitable approach to fulfill this aim would be a prospective long-lasting study with serial monitoring of vitamin D status. This could open new fascinating therapeutic scenarios. Vitamin D supplementation would have the potentiality to become a simple and economic means to prevent fibroids growth or development.

CONCLUSION:

Lower Serum vitamin D_3 levels are significantly associated with the occurrence of uterine fibroids and serum vitamin D_3 levels inversely correlate with both uterine fibroids number and total uterine fibroids volume.

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