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Relation between vitamin D and uterine fibroid

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***Abstract*---**Background; Uterine fibroids (UFs) are benign tumors that develop from the uterus' smooth muscle cells and are mostly found in the pelvic. Aim of the work; we aimed to compare serum vitamin D level between patients, have uterine fibroids and those without. Subjects and methods; our current study included 90 females and was conducted as a case control study; 50 were diagnosed with uterine fibroid and 40 were healthy volunteers (control) during the period from July 2019 to July 2020. They were recruited from Al Zahra'a University Hospital. Serum vitamin D level was measured by ELISA. Results; Vitamin D serum concentrations were significantly lower in the studied females with UFs compared to healthy controls (mean 19.24 ±16.0 vs. 33.83 ±17.5) ng/mL in cases and controls, respectively, with a statistically significant p-value <0.001. Serum vitamin D levels have a significant, linear, negative, moderate association with uterine fibroids size. Conclusion; in our study group, reduced serum vitamin D levels were found to be inversely related to UF burden. A lack of vitamin D may be a risk factor for the incidence of uterine fibroids.

***Keywords*---**Uterine fibroids, Vitamin D, Fibroid.

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Introduction

Uterine fibroids (UFs) are benign monoclonal tumors that arise from the uterus' smooth muscle cells. They are one of the most frequent female genital tract pathologies. UFs affect 5–70% of all women and are more prevalent in particular populations, with age and race serving as the primary risk factors [1]. The size, location, and symptoms of a uterine fibroid differ widely. The majority of tumors are asymptomatic, but about one-quarter to one-third of women who are impacted experience a variety of chronic and severe symptoms [2].

In spite of their undeniable impact on patient quality of life, these are frequently ignored. Furthermore, the financial load on healthcare budgets is significant, comprising the costs of presurgical diagnostics, operative therapy, time of hospitalization, job absenteeism, medications, medical worker pay, and control visit expenditures [3]. The ideal therapy would minimize the loss of blood and tumor load while retaining the women's fertility. Less invasive procedures could be provided to women who want to keep their uterus [4]. However, several of them will need future re-intervention [5].

Because the origins of UFs are multifactorial, there have been no particular preventative techniques available at this time. Several efforts have been made to develop low-cost, safe, and efficient prophylactic techniques, but they are currently in the initial phases [6]. Vit D is a collection of steroid chemicals that have a significant effect on several human body parts, such as the musculoskeletal, neurological, and immunological systems, as well as the genital tract. Vitamin D is thought to control cellular proliferation and differentiation, as well as prevent angiogenesis and promote apoptosis [7].

Vitamin D regulates the cell cycle and differentiation and has anti-angiogenic properties. Vit D insufficiency is a significant risk factor in the UFs' development. There have been a lot of theories on how vitamin D can be used to prevent UF or as a long-term treatment, but there aren't many clinical trials in this field right now [6]. Vitamin D operates through a particular type of receptor known as the VDR. It acts as a mediator of this vitamin's pleiotropic impact.

Via steroid transcriptional mechanisms, vitamin D mediates its metabolic activities [8]. This vitamin has the ability to inhibit cell proliferation, differentiation, as well as apoptosis by modulating the expression of different genes in a tissue-specific way. Such mechanisms, like those in UF, can help to inhibit neoplastic transformation and tumor growth [9]. The existing scientific data reinforces the idea of vitamin D supplementation being a cancer-preventive approach, as per Grant's review [10]. Given this, vitamin D, which plays a key part in UF biology, could be the solution [11].

Vitamin D's different impacts are mostly mediated by activating vitamin D receptors (VDRs). In this respect, VDRs are found in myometrial, endometrial, as well as UL monoclonal tumor cells. Prior studies have shown that the active metabolite of vitamin D can reduce transforming growth factor beta (TGF-β), which plays a role in the progression and development of UL [12].

Patients and Methods

Our current study is a case-control study that included 90 females, 50 of whom had uterine fibroids and 40 healthy volunteers who were age and gender matched as a control group. They have been recruited from Al Zahra'a University Hospital during the period from July 2019 to July 2020.
Inclusion criteria: Female aged (20-50) multi-parity or nulli-para. Patient group were diagnosed with uterine fibroid according to 2D ultrasound.
Exclusion criteria: Patient's refusal, continued vitamin D supplementation for other clinical causes (example, osteoporosis), females having other gynecological diseases (example, adnexal or endometrial pathology), unexplained infertility, chronic renal disease and hyperparathyroidism.
Ethical Approval: Approval of ethical committee No. (RHDIRB 2018122001) was obtained from quality education assurance unit, faculty of medicine, Al-Azhar University, Egypt.

Verbal consent was taken from all cases and controls a before participation in this study. The nature and aim of this work were fully discussed to all women who agreed to participate in the study.
Any participating patient had the right to withdraw from the study without being adversely impacted regarding the medical service she received.
The selected subjects were divided into 2 groups: Group I (n=50) [cases group]: This group included 50 Patients with fibroid. Group II (n=40) [control group]: This group included 40 Normal patients without fibroid

All subjects were exposed to the following

(1) Complete history taking (age –marriage period-parity-number of living babies-medical history).
(2) A comprehensive clinical evaluation includes a general and a local examination.
(3) 2-D Trans abdominal or Trans vaginal ultrasound examination will be performed to confirm diagnosis of uterine fibroid and to detect: Fibroid numbers, fibroid size: (In two planes, the fibroid's greatest dimensions have been measured.) The area of the fibroid has been calculated by multiplying these two dimensions together: (Area of fibroid = dimension 1 × dimension 2), fibroid site, and no other endometrial diseases or other adnexal diseases were confirmed.
(4) Blood sampling (under full aseptic conditions, five mL of venous blood was extracted and left for 30 minutes, centrifuged, separated and stored for vitamin D assay using Elisa kits which were delivered by EDI company [LOT. No
(VDK036), REF. (KT815) measurement of vitamin D was done on ELISA system (reader A31851 and washer {909} from DAS(Italy)according to manufacturer's instruction.

Vitamin D assay principle

Employing the competitive immunoassay technique, this ELISA kit is conceived, manufactured, and produced for the quantitative detection of total 25-OH Vit

D2/3 in serum. This assay employs a monoclonal antibody which binds equally to 25-OH Vit D2 and 25-OH Vit D3.

(5) Full laboratory investigations were done, including a full blood picture, kidney function tests, and hepatic function tests.

Statistical Methods

The data gathered was coded, then input and analyzed with SPSS version 22 (Statistical Package for Social Science). For categorical variables, descriptive statistics were calculated employing frequencies and percentages, and numerical variables were calculated employing mean and standard deviation (mean ± SD).

Results

The age of Participants were ranged from (22) to (49) years.

Table (1):
Basic Characteristics of the studied participants; (N= 90):

Characteristics	Studied Participants			*p-value**
	Fibroid Cases N= 50	Healthy Controls N= 40	Total N= 90	
Age; (years)				
Mean ±SD	36.34 ±7.28	36.87 ±7.14	36.57 ±7.18	0.728[a]
Minimum	22.0	22.0	22.0	
Maximum	49.0	49.0	49.0	
Parity; (No)				
Mean ±SD	2.82 ±1.83	2.57 ±1.67	2.71 ±1.76	0.515[a]
Minimum	0.00	0.00	0.00	
Maximum	9.00	6.00	9.00	
Medical Disorders; N (%)				
No	41 (82.0)	36 (90.0)	77 (85.6)	0.371[b]
Yes	9 (18.0)	4 (10.0)	13 (14.4)	
HTN	*4 (8.0)*	*1 (2.5)*	*5 (5.60)*	
DM	*5 (10.0)*	*3 (7.5)*	*9 (10.0)*	
History of Previous Surgery; N (%)				
No	34 (68.0)	35 (87.5)	64 (71.1)	0.493[b]
Yes	16 (32.0)	5 (12.5)	26 (28.9)	
CS	*10 (20.0)*	*4 (10.0)*	*14 (15.6)*	
Myomectomy	*5 (10.0)*	*1 (2.50)*	*6 (6.7)*	
Laparoscopy	*1 (2.0)*	*0 (0.00)*	*1 (1.1)*	

**p-value ≤0.05 was deemed statistically significant.*

[a] *Statistical analysis was performed by an Independent Sample t-test*

[b] *Statistical analysis was carried out by Chi square test*

Both groups were matched regarding their ages with no statistically significant difference (p-value >0.05).

Table (2)
Comparison of serum vitamin D levels in uterine fibroid cases and healthy controls (N= 90):

	Studied Participants			
	Fibroid Cases N= 50	Healthy Controls N= 40	Total N= 90	*p-value*
Serum 25-(OH) vitamin D (Vit D) levels; (ng/mL)				
Mean ±SD	19.24 ±16.0	33.83 ±17.5	25.72 ±18.1	<0.001*
Minimum	5.00	5.00	5.00	
Maximum	77.90	77.20	77.90	

**p-value ≤0.05 was deemed statistically significant.*
Statistical analysis was performed by an Independent Sample t-test

Table (2) demonstrates comparison of serum vitamin D level between studied cases with uterine fibroid and healthy controls. Vitamin D levels in the serum were significantly lower among studied females with UFs as compared with healthy controls (mean 19.24 ±16.0 vs. 33.83 ±17.5) ng/mL in patients and controls, respectively, with a statistically significant p-value <0.001.

Table (3)
Correlation between serum vitamin D level and Uterine Fibroid Size (Area of fibroid) among studied cases; (N= 50):

		Uterine Fibroid Size (Area of fibroid); (mm)
Serum 25-(OH) vitamin D (Vit D) levels; (ng/mL)	r	-0.308
	p-value	0.029*

r: Pearson Correlation Coefficient
**p-value ≤0.05 was considered statistically significant.*

Table (3) illustrates the association between serum vitamin D level and Uterine Fibroid Size (Area of fibroid) among studied females with uterine fibroid. According to persons correlation coefficient analysis; there is significant linear negative moderate association between serum vitamin D level and Uterine Fibroid Size (Area of fibroid); (r= -0.308, p-value= 0.029).

Table (4)
Correlation between serum vitamin D level and Age (years) among studied population; (N= 90):

		Age (years)
Serum 25-(OH) vitamin D levels; (ng/mL)	r	-0.136
	p-value	0.201

r: Pearson Correlation Coefficient
**p-value ≤0.05 was considered statistically significant.*

Table (4) illustrates the association between serum vitamin D level and participants' age. According to persons correlation coefficient analysis; there is non-significant correlation between serum vitamin D level and participants' age; but value of correlation coefficient (r) and its direction was recorded for screening purposes (r= -0.136, p-value= 0.201).

Table (5)
Correlation between serum vitamin D level and Parity among studied population; (N= 90):

		Parity
Serum 25-(OH) vitamin D (Vit D) levels; (ng/mL)	r	-0.106
	p-value	0.320

r: Pearson Correlation Coefficient
**p-value ≤0.05 was considered statistically significant.*

Table (5) illustrates the association between serum vitamin D level and participants' parity. According to persons correlation coefficient analysis; there is non-significant correlation between serum vitamin D level and participants' parity; but value of correlation coefficient (r) and its direction was recorded for screening purposes (r= -0.106, p-value= 0.320).

Discussion

Vitamin D is a prohormone that is created in the skin as a result of a sunlight-induced reaction and is metabolically transformed into the active metabolite 1,25-dihydroxyvitamin D3 [1,25 (OH) 2D3], primarily in the kidneys and liver. Local generation of 1,25(OH)2D3 is influenced by circulating precursor levels that could elucidate the link between vitamin D insufficiency and a variety of illnesses. VDR has been found in a variety of human tissues, which include the skin, brain, pancreas, colon, and breast, and also activates T and B lymphocytes, monocytes, and macrophages, indicating that Vit D has a variety of functions. VDR expression in the endometrium and myometrium of the female uterus, as well as UF tissues, has been shown by the researchers and others during the menstrual period [13].

The aim of this research was to evaluate the levels of vitamin D in the serum of patients having uterine fibroids and patients don't have uterine fibroids. The participants' ages ranged from 22 to 49 years old. There have been no statistically significant differences between the studied groups as regards age, parity, medical disorders, and history of previous surgery.

Our results were supported by study of Hajhashemi et al., (2019) [14] as they reported that demographic characteristics such as age (P=0.592), BMI (P=0.841), and age at menarche (P=0.731) were similar in both groups. Furthermore, during a prospective observational cross-sectional investigation, Oskovi Kaplan et al. (2018) [15] evaluated the connection between serum 25-hydroxy vitamin D levels and the hazard of UFs in premenopausal women in the Turkish population. There were 68 women who had at least one uterine leiomyoma ≥10 millimeters, compared to 56 control subjects.

In regards to age, body mass index, gravidity, as well as parity number, the groups were similar, so this study is in agreement with our study.

The present study showed that as regard distribution of the uterine fibroid among studied females with fibroid. Area of fibroid was ranged from (2.40) to (396.00) with an average fibroid area of (73.29 ±97.2) mm. regarding fibroid sites; half the studied cases had Intramural fibroid (25 cases, 50%), followed by multiple fibroids in (13 cases, 26%), Sub-mucus fibroid was in (9 cases, 18%) and sub-serous fibroids were only in (3 cases, 6%).

However, in the study of Paffoni et al. (2013) [16], on 154 patients, they reported that the incidence of intramural, sub serosal, and submucosal was (67%), 73 (32%), and 2 (1%) patients, respectively. The fibroids had a mean ± SD diameter of 19 ± 11 mm, while the bigger lesions had a mean ± SD diameter of 19 ± 11 mm for each lady, so this study is different from our study in terms of prevalence of fibroid sites and average fibroid area.

The current study showed that when serum vitamin D concentrations were examined between females with UFs and healthy controls, serum vitamin D concentrations were significantly lower in females with UFs than in healthy controls (mean 19.24 ±16.0 vs. 33.83 ±17.5) ng/mL in cases and controls respectively with a statistically significant p-value <0.001.

Our findings were in agreement with study of Paffoni et al., (2013)[16] as they reported that the occurrence of leiomyomas is up to twofold greater in women suffering from vitamin D insufficiency, defined as a serum level of 25-hydroxyvitamin D3 less than 10 ng/mL. Also our findings are consistent with those of Sabry et al. (2013) [17], who selected 104 patients with fibroids and 50 healthy controls and found that the cases had significantly lower concentrations of 25-hydroxyvitamin D3 than the controls (19.7 ± 11.8 versus 22.3 ± 6.5 ng/mL, P = .01).

In the same line**,** Baird et al., (2013) [18] retrospectively analyzed preserved plasma specimens from 1036 women (674 had leiomyomas and 362 unaffected controls) and found that those having adequate vitamin D concentrations (> 20 ng/mL) exhibited a 32% lower risk of leiomyomas (OR = 0.68, 95% CI = 0.48–0.96).

According to Singh et al., (2019) [19], they discovered that fibroid patients had significantly lower serum vitamin D3 concentrations than the control group (10.81 ± 6.18 versus 22.91 ± 16.18, $p \leq 0.0001$). According to Srivastava et al. (2020) [20], the mean ± SD level of 25-hydroxyvitamin D3 in patients was significantly lower than in controls (15.10 ± 6.09 versus 26.09 ± 7.90 respectively, $p < 0.001$). In patients and control, the percentage of women having 25-hydroxyvitaminD3 insufficiency was 9 (20%) and 3 (6.67%), respectively ($p < 0.001$). This study follows in the same line as ours.

Also, Mohammadi et al. (2020) [21] reported that the present meta-analysis comprised 9 eligible trials with a total of 1730 individuals (835 cases having UL and 895 controls). According to pooled data from random influence modeling,

serum vitamin D concentrations in women with UL were significantly lower compared to the control group (n = 9, SMD = − 0.67; 95% CI, − 0.98, − 0.35, p < 0.001; I2 = 89.3%, p < 0.001).

When comparing the frequency of vitamin D insufficiency in the general population, Leigh et al. (2018) [22] found that women having UFs had an elevated incidence of vitamin D insufficiency throughout the boards. They additionally exhibit a mean 25 (OH) vit D concentration of 23.3ng/ml, lending credence to the idea that poor vit D concentrations may be a risk factor for fibroid growth and development.

In our study, as regard correlation between serum vitamin D level and Uterine Fibroid Size (Area of fibroid) among studied females with uterine fibroid. There is significant linear negative moderate association between serum vitamin D level and Uterine Fibroid Size (Area of fibroid); (r= -0.308, p-value= 0.029). As regard correlation between serum vitamin D level and participants' age, there is non-significant correlation between serum vitamin D level and participants' age. Also correlation between serum vitamin D level and participants' parity, there is non-significant correlation between serum vitamin D level and participants' parity.

Our results were supported by study of Sabry et al., (2013)[17] as they reported that serum 25-OHD concentrations were shown to be inversely linked to the volume of UFs in their investigation of 104 women having UFs and 50 control subjects. In contrast, no significant differences in serum 25OHD between various fibroid sizes have been discovered in research conducted by Baird et al. (2013) [18], in which women with UFs were grouped as per the diameter of the biggest uterine fibroid (non-fibroids, small fibroids [diameter < 4 cm], big fibroids [diameter ≥4 cm], with a 4-cm diameter as the cut-off. Various approaches for calculating the size of UFs may be to blame for the discrepancy. So this study is in disagreement with our study in detecting size of fibroid with a 4-cm diameter as cut off.

Furthermore, Singh et al. (2019) [19] revealed that serum vitamin D3 concentrations were lower in women with more than three fibroids compared to individuals with fewer than three fibroids. Despite this, the difference was not statistically significant (9.36 ± 5.77 versus 11.24 ± 6.22; p = 0.26). They were unable to detect a link between the greatest fibroid's volume and serum vitamin D3 concentrations.

Conclusion

In our study group, lower serum vitamin D concentrations were found to be inversely associated with uterine fibroid size. A lack of vitamin D may increase the risk of uterine fibroids occurring.

Conflict of Interest: The Authors state that they have no conflicts of interest

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References

1. Al-Hendy, A., Myers, E. R., & Stewart, E. Fibroids: Uterine Fibroids: Burden and Unmet Medical Need. In *Seminars in reproductive medicine*. 2017; 35(6): 473.
2. Stewart, E. A., Cookson, C. L., Gandolfo, R. A., & Schulze-Rath, R. Epidemiology of uterine fibroids: a systematic review. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2017; *124*(10), 1501-1512.
3. Soliman, A. M., Margolis, M. K., Castelli-Haley, J., Fuldeore, M. J., Owens, C. D., & Coyne, K. S. Impact of uterine fibroid symptoms on health-related quality of life of US women: evidence from a cross-sectional survey. *Current medical research and opinion*. 2017; *33*(11), 1971-1978.
4. Wu, H. Y., & Wang, K. C. Minimally invasive approaches to the surgical management of fibroids. In *Seminars in reproductive medicine*. 2017; 35(06): 533-548.
5. Borah, B. J., Yao, X., Laughlin-Tommaso, S. K., Heien, H. C., & Stewart, E. A. Comparative effectiveness of uterine leiomyoma procedures uses a large insurance claims database. *Obstetrics and gynecology*. 2017; *130*(5): 1047.
6. Ciebiera, M., Łukaszuk, K., Męczekalski, B., Ciebiera, M., Wojtyła, C., Słabuszewska-Jóźwiak, A., et al. Alternative oral agents in prophylaxis and therapy of uterine fibroids—an up-to-date review. *International journal of molecular sciences*. 2017; *18*(12): 2586.
7. Holick, M. F. Vitamin D deficiency. *New England Journal of Medicine*. 2007; *357*(3): 266-281.
8. Kato, S. The function of vitamin D receptor in vitamin D action. *The Journal of Biochemistry*. 2000; *127*(5), 717-722.
9. Ylikomi, T., Laaksi, I., Lou, Y. R., Martikainen, P., Miettinen, S., Pennanen, P., et al. Antiproliferative action of vitamin D, 2002.
10. Grant, W. B. A review of the evidence supporting the vitamin D-cancer prevention hypothesis in 2017. *Anticancer research*. 2018; *38*(2), 1121-1136.
11. Brakta, S., Diamond, J. S., Al-Hendy, A., Diamond, M. P., & Halder, S. K. Role of vitamin D in uterine fibroid biology. *Fertility and sterility*. 2015; *104*(3): 698-706.
12. Halder SK, Goodwin JS, Al-Hendy A. 1, 25-Dihydroxyvitamin D3 reduces TGF-β3-induced fibrosis-related gene expression in human uterine leiomyoma cells. J Clin Endocrinol Metab. 2011; 96(4):E754–E62.
13. Feng L, Jayes FL, Jung SH, Leppert PC. Vitamin D receptor (VDR) is over-expressed in the center of uterine fibroids. Fertil Steril. 2010; 94(4):S75.
14. Hajhashemi, M., Ansari, M., Haghollahi, F., & Eslami, B. The effect of vitamin D supplementation on the size of uterine leiomyoma in women with vitamin D deficiency. Caspian journal of internal medicine. 2019; 10(2), 125.
15. Oskovi Kaplan, Z. A., Taşçi, Y., Topçu, H. O., & Erkaya, S. 25-Hydroxy vitamin D levels in premenopausal Turkish women with uterine leiomyoma. Gynecological Endocrinology. 2018; 34(3), 261-264.
16. Paffoni, A., Somigliana, E., Vigano', P., Benaglia, L., Cardellicchio, L., Pagliardini, L., et al. Vitamin D status in women with uterine leiomyomas. The Journal of Clinical Endocrinology & Metabolism. 2013; 98(8), E1374-E1378.
17. Sabry M, Halder SK, Allah AS, Roshdy E, Rajaratnam V, Al-Hendy A. Serum vitamin D3 level inversely correlates with uterine fibroid volume in different

ethnic groups: a cross-sectional observational study. Int J Womens Health. 2013; 5:93–100.
18. Baird, D. D., Hill, M. C., Schectman, J. M., & Hollis, B. W. Vitamin D and risk of uterine fibroids. *Epidemiology (Cambridge, Mass.)*. 2013; *24*(3), 447.
19. Singh, V., Barik, A., & Imam, N. Vitamin D 3 Level in Women with Uterine Fibroid: An Observational Study in Eastern Indian Population. *The Journal of Obstetrics and Gynecology of India*. 2019; *69*(2), 161-165.
20. Srivastava, P., Gupta, H. P., Singhi, S., Khanduri, S., & Rathore, B. Evaluation of 25-hydroxy vitamin D3 levels in patients with a fibroid uterus. Journal of Obstetrics and Gynaecology. 2020; 40(5), 710-714.
21. Mohammadi, R., Tabrizi, R., Hessami, K., Ashari, H., Nowrouzi-Sohrabi, P., Hosseini-Bensenjan, M., et al. Correlation of low serum vitamin-D with uterine leiomyoma: a systematic review and meta-analysis. *Reproductive Biology and Endocrinology*. 2020; *18*(1), 1-8.
22. Leigh D Rosen, Suzanne K Fenske, Heather M Isola and Charles J Ascher-Walsh. Vitamin D deficiency in women with uterine fibroids versus Vitamin D deficiency in the general population. Clin Obstet Gynecol Reprod Med. 2018; 4(6): 3-3.
23. Makariou S, Liberopoulos EN, Elisaf M. Novel roles of vitamin D in disease: what is new in 2011? Eur J Intern Med. 2011; 22:355–62.