ORIGINAL RESEARCH REPORT

Risk of uterine fibroid in patients with Vitamin D deficiency: A cross-sectional study

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ABSTRACT

Background: Uterine fibroids (UFs) are common benign tumors in women, and their etiology is influenced by multiple factors. A cross-sectional study was conducted to investigate levels of Vitamin D in patients with UFs and explore the potential association between UF symptoms and Vitamin D levels. **Methods:** The study included 117 subjects: 50 healthy controls and 67 UF cases. Abdominal or transvaginal ultrasonography was conducted to confirm the diagnosis and assess the number, size, and sonographic appearance of the lesions. Blood samples were collected to measure 1,25-dihydroxycholecalciferol (D_3) levels using an enzyme-linked immunosorbent assay kit. Multiple logistic regression analysis was used to estimate crude and adjusted odds ratios (AORs) with 95% confidence intervals (CIs) for the risk of UFs. **Results:** After adjusting the potential confounders, women with high levels of Vitamin D were associated with a lower likelihood of UFs (AOR = 0.97; 95% CI: 0.93–0.99); and the odds of UF had decreased by 3% per unit increase in the level of Vitamin D. However, there were no significant differences in Vitamin D levels based on lesion location, size, or UF-related symptoms. Similarly, an inverse relation was observed between increasing body mass index and the UF (AOR = 0.84; 95% CI: 0.75–0.95). Although advanced aged and menarche, employed women, and economic status (lower) increased the risk of UF, there were no significant associations ($P > 0.05$). **Conclusion**: Findings showed that a high level of Vitamin D is associated with a reduced risk of UFs.

Key words: Gynecology, oncology, uterine fibroid, Vitamin D, women health

INTRODUCTION

Uterine fibroids (UFs), also known as uterine leiomyomas, are benign monoclonal tumors that originate from smooth muscle cells of the uterus and are predominantly located in the pelvic region. These tumors are one of the most common pathologies observed in the female reproductive system and are generally found in 5%–70% of women.[1,2] The findings of the global burden disease study indicate a significant increase in the incidences and disability-adjusted life years of UFs worldwide between 1990 and 2019. However, there was no significant growth observed in UF-related deaths during this period. It is noteworthy that lower sociodemographic regions experienced a growing burden of UFs, adding to the existing challenges.[3] Their occurrence within a community is age and race-dependent, making these factors among the primary risk factors for UFs development.[4,5] UFs are mainly observed during women's reproductive years and are not seen in prepubertal girls, indicating a hormone-dependent origin of the tumor.[6] UFs typically vary in size, location, and clinical symptoms.[7] While most cases of these tumors remain asymptomatic, approximately one-fourth to one-third of affected women experience severe and chronic symptoms.[8] These symptoms include abnormal and excessive uterine bleeding, gastrointestinal issues such as bloating and constipation, urinary problems, irondeficiency anemia, abdominal and pelvic pain, infertility, and obstetric complications such as miscarriage and preterm labor.[9,10] If conservative treatments fail to alleviate symptoms in

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patients with clinically symptomatic UF tumors, surgical intervention may be considered.[11] There are various surgical methods available for UF treatment, and an ideal approach should reduce bleeding and tumor burden while preserving fertility.[12,13]

Recent studies have shown multiple factors associated with an increased risk of UFs in patients, but there are also contradictions among the results of these studies. Various factors have been identified as contributing to the development of UFs. These factors include being of African American race, having a high body mass index (BMI), being of advanced age, being in a premenopausal stage, having hypertension, having a positive family history of UFs, the length of time since the last childbirth, the use of dietary supplements, and the consumption of soy milk.[4] Hypovitaminosis D and Vitamin D deficiency contribute to the development of UFs.[14]

The etiology of UFs is typically multifactorial, and as of now, there is no precise preventive method established.[15] Several attempts have been made to develop cost-effective, safe, and efficient preventive approaches for UFs, but these strategies are still in the early stages of development.[16] Vitamin D is among the factors that significantly influence the biology of UFs. It belongs to a group of fat-soluble, steroid-like substances that exert considerable effects on the body. Receptors for Vitamin D are found in various organs, including the myometrium and UF tumor tissue.[17] New research has brought attention to the abnormal low levels of Vitamin D as a main cause of UFs.[18] Studies have found that women with UFs have significantly lower levels of Vitamin D in their blood compared to women without UFs. This finding has been confirmed in both Turkish and African American populations.[19] In addition, cultural and environmental differences such as clothing also contribute to the development of UFs and can play a major role.[20]

Since Vitamin D appears to play a significant role in UFs cases, the objective of this study is to compare the levels of Vitamin D in patients with UFs and individuals without the condition, and explore the potential association between symptoms of UFs and Vitamin D levels.

METHODS

A cross-sectional study was conducted between January 2021 and May 2022 at Al-Zahra Hospital in Tabriz, Iran. Female patients who were referred to Al-Zahra Hospital in Tabriz, Iran were selected for inclusion in the study. The case group consisted of patients with UFs who had medical records at Al-Zahra Hospital. The controls were healthy participants randomly selected from outpatients visiting the hospital clinic for reasons unrelated to fibroid lesions. Al-Zahra Hospital is a large referral educational, research, and treatment center located in the northwest of Iran, serving the general population across several provinces. The subjects in the control group were patients referred to the clinics of this hospital for reasons unrelated to UFs, drawn from the general population. Laboratory, clinical, and paraclinical assessments were performed for all controls, and they did not have any UFs.

The sample size was determined using pilot study results for Vitamin D levels in the case and control groups (25 ± 12 and 33 ± 15 ng/ml, respectively). Considering the odds ratio (OR = 0.68) from a previous study,[21,22] along with α =0.05 and β =0.8, a total of 50 subjects (100 samples in total) were estimated. The study ultimately involved 117 subjects to enhance study power and account for nonresponses.

The inclusion criteria for the study were as follows: individuals aged between 20 and 49 years, willingness to participate in the research, and a definitive diagnosis of UF confirmed through ultrasonography. On the other hand, menopausal women, patients who declined to participate, pregnant women, individuals with a previous diagnosis of any form of malignancy, those with a family history of fibroid lesions, and those taking Vitamin D supplements or medications that affect Vitamin D levels (such as phenytoin) were excluded from the study. Detailed information regarding the research objectives and procedures was provided to the patients, and written informed consent was obtained from each participant after a thorough explanation. The ethical protocols for this study have been duly approved by the Ethical Committee of Tabriz University of Medical Sciences (approval code: IR.TBZMED.REC.1400.1021).

The diagnosis was confirmed through the use of abdominal or transvaginal ultrasonography, which was conducted by a skilled radiologist at the hospital. In addition, data regarding the number, size, and sonographic appearance of the lesions were extracted from the ultrasound scans.

The blood samples were collected from all participants and after isolation of serum, to assess 1,25dihydroxycholecalciferol (D3) levels were measured using the commercial enzyme-linked immunosorbent assay kit. Vitamin D deficiency was considered serum 25-hydroxyvitamin D <50 nmol/L or 20 ng/ml.[22-27] Moreover, the necessary information was collected including age, gravidity, parity, weight, height, regularity of periods, socioeconomic status, literacy, age of menarche, history of miscarriage, medications, nutrition, medical history of other diseases, and presence of complications related to fibroid lesions (such as pelvic pain, excessive bleeding, infertility, and compressive effects on nearby organs). The study compared these covariates between the case and control groups.

Socioeconomic status was assessed using a validated instrument grounded in native studies from Iran.[26-29]

Economic status was determined by gross monthly household income from all sources, measured in Iranian currency (Rials), and categorized into: less than 10 million, 10–30 million, and over 30 million Rials. Educational level was evaluated based on years of education and classified as primary school, secondary school, and high school or higher education.

Dietary intake of the participants was measured using Iranian validated semiquantitative Food Frequency Questionnaire.[24] This tool has been validated in Iran. Participants were asked to report the frequency of consumption of a given serving of each food item on a daily, weekly, monthly, and yearly basis and data were then converted to daily intake unites. Based on the standard food pyramid, daily consumption of more than 3 units of meat group, more than 10 units of cereals, and more than 2 units of fats group was considered a high-protein, high-calorie, and high-fat intake, respectively.[26-28]

The SPSS software version 22.0 (Chicago, IL, USA) was used for data analysis. The Kolmogorov–Smirnov test was used to check data normality. Categorical variables underwent examination using the Chi-square test. *t*-test was carried out to assess quantitative variables or Mann–Whitney test, when data distribution was not normal. To compare multiple locations of fibroid lesions, analysis of variance was employed alongside the least significant difference for *post hoc* analysis. For adjusting potential confounders in the association between UF and Vitamin D level and to calculate true effect size (measure of association), multiple logistic regression analysis was used to estimate crude and adjusted ORs (AORs) with 95% confidence intervals (CIs) for the risk of UFs. For model building, all independent variables were first assessed with univariate analysis. Then, all variables with $P < 0.2$ were analyzed with multiple logistic regression using "*Enter*" method. The Hosmer and Lemeshow statistic was used for checking the goodness of fit with the model.

RESULTS

During the study period, a total of 119 women were initially enrolled. However, two individuals later decided to withdraw from the study, resulting in a final sample size of 117 women. Among these participants, there were 67 individuals with UFs and 50 healthy controls.

Table 1 shows the baseline and demographic characteristics of the participants. There were significant differences regarding women age, BMI, type of women employment, or homemakers and age of menarche ($P < 0.05$). However, there was no significant difference in serum Vitamin D levels between women with normal and abnormal menstrual cycles ($P = 0.510$), different gravities ($P = 0.110$),

Table 1: Demographic and baseline characteristics of the participants

Variables	Control group (*n*=50)	Case group (uterine fibroids) (*n*=67)	*P*
Age (year), mean±SD	40.32±8.42	43.27±5.95	0.033
BMI (kg/m^2), mean±SD	26.95±3.08	28.32±4.34	0.002
Gravidity, *n* (%)			
Nulliparous	7 (14)	6 (9)	0.687
Primiparous	6 (12)	9 (13.4)	
Multiparous	37 (74)	52 (77.6)	
Parity, *n* (%)			
Null parity/low	10 (20)	10 (14.9)	0.428
Multiparty (1–3)	35 (70)	45 (67.2)	
Grand multipara (4–8)	5 (10)	12 (17.9)	
Menstrual cycles, *n* (%)			
Regular	15 (30)	23 (34.3)	0.385
Irregular	35 (70)	44 (65.7)	
Literacy, *n* (%)			
Illiterate and/or preliminary	6 (12)	10 (14.9)	0.815
Secondary school	22 (44)	31 (46.3)	
High school or	13 (26)	18 (26.9)	
Academic	9 (18)	8 (11.9)	
Employment state, *n* (%)			
Homemaker	40 (80)	62 (92.5)	0.043
Employed	10 (20)	5 (7.5)	
Financial state (million Rial)*, *n* (%)			
Low income (<10)	12 (24)	25 (37.3)	0.074
Middle income (10–30)	38 (76)	39 (58.2)	
High income (≥30)	0	3 (4.5)	
Physical activity, *n* (%)			
Sedentary or light activity	18 (36)	27 (40.3)	0.390
Moderately active	32 (64)	38 (56.7)	
Vigorously active	0	2 (3)	
Sunlight exposure (h/day), *n* (%)			
<1	5 (10)	4 (6)	0.133
1–2	26 (52)	29 (43.3)	
2–4	17 (34)	34 (50.7)	
>4	2 (4)	0	
Age of menarche (years), *n* (%)			
Early (≤10)	0	0	0.031
Normal (11–14)	50 (100)	65 (97)	
Late (≥15)	0	2 (3)	
Miscarriages, n (%)			
Never	35 (70)	44 (65.7)	0.808
Single	12 (24)	17 (25.4)	
Multiple (≥2)	3 (6)	6 (9)	
Dietary intake, n (%)			
Normal	4 (8)	4 6()	0.757
High protein	21 (42)	27 (40)	
High calorie	20 (40)	32 (47.8)	
High fat	5 (10)	4 (6)	
Vitamin D (ng/mL), mean±SD	33.2±17.6	26.6±12.2	0.027
Vitamin D deficiency (ng/mL)			
<20	11 (22)	22 (32.8)	0.042
≥20	39 (78)	45 (67.2)	

*Million Rials (Iranian). BMI=Body mass index, SD=Standard deviation

different parity histories (P = 0.752), different literacy levels (P = 0.343), different levels of physical activity (P = 0.296), different sunlight exposures (P = 0.102), and history of abortion (P = 0.731). Nonetheless, Vitamin D levels were significantly higher in women with high income (56.66 ± 19.96) compared to women with middle (29.15 ± 15.48) and low (30.92 ± 14.80) income (P = 0.008 and P = 0.017, respectively). In addition, Vitamin D levels were significantly lower in women with a high-fat diet (18.40 ± 6.51) compared to women with a normal diet (39.23 ± 17.90) and high-calorie diet (33.62 ± 18.12) (P = 0.029 and P = 0.033, respectively).

Concerning Vitamin D levels, the overall proportion of Vitamin D deficiency (<20 ng/ml) was 32.8% in the case group and 22% in the control group. In addition, the mean values of Vitamin D were 33.2 in the control group and 26.6 in the case group, respectively, with this difference being statistically significant (P = 0.027).

In the case group, 41 (62%) and 23 (34.32%) of patients had bleeding pelvic pain, respectively. The distribution of UFs patients based on the location of leiomyoma is presented in Table 2. The highest proportion of lesions was observed in the intramural region, with approximately 57% of patients having leiomyoma in this area. In addition, around 22% of UFs patients had lesions in multiple locations.

Regarding the serum Vitamin D levels among patients with lesions in different locations, the results indicated no significant differences [P = 563; Table 3]. Our results showed no significant correlation between the diameter of the largest fibroid and Vitamin D levels in the patient group (P = 0.910, r = −0.014).

Table 4 indicated that the results of multiple logistic regression analysis and adjusted ORs with 95% CIs for the odds of UFs in the association between UFs and levels of Vitamin D. After adjusting the potential confounders, women with high levels of Vitamin D was associated with lower odds of UFs (AOR = 0.97; 95% CI: 0.93–0.99). In other words, the odds of UF had decreased by 3% per unit increase in the level of Vitamin D, adjusted for all other variables in the model. Similarly, an inverse relation was observed between increasing BMI and the odds of UF (AOR = 0.84; 95% CI: 0.75–0.95). Although advanced age AOR = 1.1 (0.97–1.22) and menarche age AOR = 0.28 (0.07–1.15), employed women AOR = 2.24 (0.66–7.5), and economic status (lower) AOR = 1.64 (0.7–3.8) were increased the odds of UF, while there were no significant associations.

Table 2: Frequency of patients based on the location of the leiomyomas

	Uterine fibroid patients (n=67), n (%)
Intramural	38 (56.7)
Subserosal	9 (13.4)
Submucosal	5 (7.5)
Hybrid	15 (22.4)

Table 3: Serum levels of total 25(OH) D according to the location of the leiomyomas

	Intramural (n=38)	Subserosal (n=9)	Submucosal (n=5)	Hybrid (n=15)
Total 25(OH) D (ng/mL)	35.76±18.46	29.24±12.95	33.94±11.99	28.97±19.71
P	0.563			

DISCUSSION

Various factors have been recognized as playing a role in the formation of UFs, such as ethnicity, elevated BMI, older age, being in the premenopausal stage, hypertension, having a family history of UFs, time elapsed since last childbirth, the use of dietary supplements, and the consumption of soy milk.[30] In addition, insufficient levels of Vitamin D and a deficiency in this essential nutrient have also been linked to the occurrence of UFs.[31]

Vitamin D is an important compound that has a significant impact on the body. It is a fat-soluble substance with properties similar to steroids. Vitamin D receptors can be found in different organs, including the myometrium and UF tumor tissue.[32] In this study, we aimed to compare the levels of Vitamin D in patients with UFs and individuals without this condition. We found that the patient group had significantly lower levels of serum Vitamin D compared to the control group. This finding in agreement with previous studies that have consistently shown that women with UFs have lower levels of Vitamin D in their blood compared to women without UFs, which has been observed in various populations.[33-35] It is suggested that the protective effects

Table 4: Association between uterine fibroids and Vitamin D levels after adjusting for the potential confounders using multiple logistic regression analysis, adjusted odds ratios and 95% confidence intervals

Variables	Crude OR; 95% CI	Adjusted OR; 95% CI
Age (years)	0.94 (0.89–0.99)	1.1 (0.97–1.22)
P	0.033	0.471
BMI (kg/m²)	0.84 (0.76–0.94)	0.84 (0.75–0.95)
P	0.002	0.003
Vitamin D (ng/mL)	0.97 (0.94–0.99)	0.97 (0.93–0.99)
P	0.031	0.041
Employment		
Housewife	1	1
Employed	3.1 (0.99–9.7)	2.24 (0.66–7.5)
P	0.053	0.195
Menarch age (upper 14 years)	0.20 (0.05–0.74)	0.28 (0.07–1.15)
P	0.016	0.078
Economic status (lower)	2.1 (0.90–4.6)	1.64 (0.7–3.8)
P	0.091	0.254

OR=Odds ratio, CI=Confidence interval, BMI=Body mass index

of Vitamin D are initiated through its regulation of estrogen and progesterone levels.[25] In addition, a recent study has found differences in the concentration of Vitamin D receptors near fibroid lesions compared to healthy uterine tissue.[36] This further supports the hypothesis of a multifactorial cause for fibroid development, which may not always be dependent on Vitamin D. To address this inconsistency, the role of Vitamin D binding protein (DBP) and variations in free Vitamin D levels should be considered. Vitamin D is primarily transported in the bloodstream bound to DBP. However, it is important to note that not all Vitamin D bound to DBP is accessible to target tissues. Only the unbound or "free" portion of Vitamin D can be utilized by cells.[36] On the other hand, research has shown higher levels of DBP in patients with UFs.[37] This increase in DBP may result in more Vitamin D being bound and transported, leading to higher total Vitamin D levels. However, it is crucial to measure the levels of free or unbound Vitamin D to determine its actual availability to target tissues. Therefore, although we found lower total Vitamin D levels in the serum of patients with fibroids, elevated levels of DBP may reduce the availability of free and active Vitamin D, potentially contributing to fibroid development.

Our study did not find any significant associations between Vitamin D levels and the size of fibroid lesions, which contradicts the findings of previous studies.[36,37] However, a recent study conducted in Turkey yielded similar results, which is particularly interesting due to the close proximity and cultural similarities between their study population and ours.[20] This suggests that the development of fibroids may be influenced by multiple factors, including genetics and the environment. Furthermore, our study did not identify any significant associations between Vitamin D levels and the location or sonographic appearance of fibroid lesions. To the best of our knowledge, no other study has investigated this aspect of UFs.

There were no notable differences in serum Vitamin D levels based on the regularity of menstrual cycles, employment status, number of pregnancies, parity history, literacy levels, physical activity levels, sunlight exposure, age of first menstruation, and history of abortion. Interestingly, we observed that women with a higher income had significantly higher levels of Vitamin D compared to those with middle and low incomes. This difference may be attributed to lifestyle and dietary choices, as individuals from high-income households have easier access to animal products rich in Vitamin D in sufficient quantities.[31] Furthermore, we found that women with a high-fat diet exhibited significantly lower levels of Vitamin D compared to those with a normal or high-calorie diet. It has been reported that Vitamin D can be stored in adipose tissue, and excessive body fatness may lead to diminished levels of Vitamin D in the bloodstream.[38,39]

Limitations

Our study had limitations. We found an association between low levels of vitamin D and the risk of UF in women. However, many covariates are associated with UF and these variables can confound the true effects of the association between Vitamin D and UF. To remove this issue, we used multiple logistic regression analysis to estimate adjusted ORs with 95% CIs for the association between UF and levels of Vitamin D after adjusting covariates and potential confounders.

CONCLUSION

Findings indicated that higher serum Vitamin D levels are reduced the risk of UF. Vitamin D deficiency is a possible risk factor for the incident of UFs meanwhile there are meta-analysis and randomized controlled trials are suggested.

Ethics approval

The study received ethical approval from the local ethics committee of Tabriz University of Medical Science, Tabriz, Iran with the following code: IR.TBZMED.REC.1400.1021. We confirm that all methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contribution

PH, SH and HA contributed to the design of the study. HA, PH, SH, AF, HZ and GJ contributed in collecting data. PH, SH, and HZ has written the first draft of this manuscript and all authors have critically read the text and contributed with inputs and revisions, and all authors read and approved the final manuscript.

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Conflicts of interest

There are no conflicts of interest.

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