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Correlation between Uterine Fibroid Volume and Vitamin D Level in Thai Women: A cross-sectional study

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ABSTRACT

Objectives: This study aimed to investigate the correlation between serum vitamin D levels and myoma uteri volume in Thai women.

Materials and Methods: This study enrolled ninety Thai women diagnosed with uterine leiomyoma. We used pelvic ultrasound to measure the total myoma volume and collected blood samples on the same day to assess serum vitamin D levels. The correlation between vitamin D levels and myoma uteri volume was then analyzed. We measured the myoma volume using the formula of width x length x height x 0.523. Vitamin D level was measured by electrochemiluminescence immunoassay.

Results: The median volume of myoma uteri was 24.57 cm^3 (max = 1946.03, min = 1.05). The median serum vitamin D level was 20.35 ng/mL (max = 46, min = 7.50). The study found a weak inverse correlation between serum vitamin D levels and myoma uteri volume, although the correlation coefficient indicated a low correlation (Pearson correlation coefficient, r = - 0.239; p = 0.023). The prevalence of vitamin D deficiency in Thai women in the study was 48.9%.

Conclusion: Serum vitamin D levels were weak and inversely correlated to the myoma uteri volume among Thai women.

Keywords: myoma uteri, vitamin D, vitamin D deficiency.

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ความสัมพันธ์ระหว่างปริมาตรเนื้องอกกล้ามเนื้อมดลูกและระดับวิตามินดีในหญิงไทย

กฤติภร มหาจิราภัทร์, สิตานัน เลิศศิริพาณิชย์

บทคัดย่อ

วัตถุประสงค์*: การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาความสัมพันธ์ระหว่างระดับวิตามินดีในเลือดกับปริมาตรของ เนื้องอกมดลูกในผู้หญิงไทย*

วัสดุและวิธีการ*: การศึกษาครั้งนี้ทำการศึกษาในกลุ่มสตรีที่อยู่ในช่วงอายุ 18-50 ปี ที่มีเนื้องอกกล้ามเนื้อมดลูก ขนาดรวมกันมากกว่า 2 เซนติเมตรขึ้นไป ที่มารับการรักษาที่แผนกนรีเวช โรงพยาบาลราชวิถี ในระหว่างเดือน กรกฎาคม 2567 - กันยายน 2567 โดยการตรวจคลื่นความถี่สูงบริเวณเชิงกราน เพื่อวัดปริมาตรรวมของเนื้องอกมดลูก คำนวณจาก ความกว้าง x ความยาว x ความสูง x 0.523 และเก็บตัวอย่างเลือดในวันเดียวกัน เพื่อตรวจสอบ ระดับวิตามินดีในเลือด ระดับวิตามินดีถูกวัดโดยใช้วิธี electrochemiluminescence immunoassay จากนั้นทำการวิเคราะห์ความสัมพันธ์ระหว่างระดับวิตามินดีและปริมาตรเนื้องอกมดลูกปริมาตรของเนื้องอกมดลูก*

ผลการศึกษา*: มัธยฐานของเนื้องอกมดลูกอยู่ที่ 24.57 ลูกบาศก์เซนติเมตร (ต่ำสุด = 1.05, สูงสุด = 1946.03) : มัธยฐานของระดับวิตามินดีอยู่ที่ 20.35 นาโนกรัมต่อมิลลิลิตร (ต่ำสุด = 7.5, สูงสุด = 46) พบว่ามีความสัมพันธ์เชิงลบอย่างมีนัยสำคัญทางสถิติระหว่างระดับวิตามินดีในเลือดและปริมาตรเนื้องอกมดลูก แม้ว่าสัมประสิทธิ์สหสัมพันธ์จะแสดงถึงความสัมพันธ์ในระดับต่ำ (สัมประสิทธิ์สหสัมพันธ์เพียร์สัน, r = - 0.239; p = 0.023) นอกจากนี้พบว่าร้อยละ 48.9 ของผู้หญิงไทยในกลุ่มตัวอย่างมีภาวะขาดวิตามินดี*

สรุป*: ระดับวิตามินดีในเลือดที่ตำลงมีความสัมพันธ์เชิงผกผันเล็กน้อยกับการเพิ่มขึ้นของปริมาตรเนื้องอกมดลูกในผู้หญิงไทย*

คำสำคัญ*: เนื้องอกมดลูก, วิตามินดี, ภาวะขาดวิตามินดี*

Introduction

Uterine fibroids are the most common smooth muscle tumors of the uterus[1], with the highest prevalence found in reproductive aged women. These fibroids contribute to about 30% of hysterectomy in women aged 18-44[2]. In Thailand, 60% of women who underwent hysterectomy were diagnosed with uterine fibroids.

The prevalence of vitamin D deficiency in Thai women with uterine fibroids was 69.6%[3]. Common presenting symptoms of uterine leiomyoma are varied by size, location and type of the fibroids, which include abnormal uterine bleeding, anemia, miscarriage[4], infertility, frequent urination, difficulty in urination[5], constipation, and difficulty with bowel movements[5].

Vitamin D can be synthesized in the skin under ultraviolet B radiation. Avoiding sunlight and applying sunscreen can decrease vitamin D synthesis[6]. Other sources of vitamin D include consumption of fatty fish, eggs and milk. Vitamin D deficiency has become more prevalent, particularly in Thai women aged 25-54, with a rate of 43.1%[8]. Interestingly, vitamin D deficiency is more common among patients with uterine fibroids compared to those without[9].

Animal and human studies suggest that vitamin D can reduce the growth rate of uterine fibroids[7]. Hypothesis of vitamin D inhibitory function in fibroid growth includes suppressing of cell growth and proliferating-related genes, antiapoptotic genes, modulation of estrogen and progesterone receptors[7] and mediation of transforming growth factor beta activities of the tumor cells[9]. Despite these findings, previous studies have shown conflicting results on the correlation between fibroid volume and the severity of vitamin D deficiency. From our extensive review, there is no study on this subject in Thailand. This research aimed to explore the relationship between uterine fibroid volume and vitamin D levels in Thai women, with the secondary outcomes of exploring the severity of vitamin D level deficiency in Thai women, and to identify other personal and environmental factors that may affect uterine fibroid volume.

Materials and Methods

Thai women aged 18-50 years old who visited the Gynecology Department of Rajavithi Hospital were recruited. The study was conducted from July to September 2024. This study was approved by the Institutional Review Board of Rajavithi Hospital (EC number 67057). The trial was completed without any protocol amendments.

The inclusion criteria consisted of Thai female patients aged 18-50 years who were diagnosed with myoma uteri size greater than 2 centimeters in total by pelvic ultrasonography (combining the largest diameter of all myoma) and were willing to participate in the research. The exclusion criteria for this study included women receiving gonadotropin-releasing hormone analogues, pregnant women, postpartum or post-miscarriage women within the past 6 weeks, breastfeeding women, and postmenopausal women. Additionally, we excluded women who had previously undergone myomectomy, those who had taken vitamin D supplements within the past 6 months, and patients with chronic kidney or liver disease. Other chronic diseases affecting vitamin D metabolism, such as thyroid or parathyroid disease, also disqualified participants.

Based on a previous study, the correlation between vitamin D levels and the size of leiomyomas was used to calculate the sample size[10]. The Pearson correlation coefficient was 0.292. Using an alpha of 0.05 and a beta of 80%, a minimum sample size of 90 patients was required.

Participants in the study were enrolled by a single researcher. Personal baseline data recorded include age (years), body mass index (BMI) (kg/m^2), underlying medical conditions, current medications, smoking history, number of children, educational level, last pregnancy, and number of children. The uterine fibroids' medical history includes the year of diagnosis, family history, prior treatments, and whether the participant has previously undergone a myomectomy. Dietary and sunlight exposure were records, along with work habits, including details on sunlight exposure, use of sunscreen, clothing habits, work activities, fish consumption, egg consumption, milk consumption, current medications, and whether vitamin D or calcium supplements have been taken in the past 6 months. The hours of sun exposure were estimated using participant surveys about the direct time spent outdoors during daylight hours. Participants will undergo blood sampling to measure their serum vitamin D levels. Additionally, a pelvic ultrasound will be performed on the day of participation by qualified specialists of Gynecology Department, Rajavithi Hospital.

The Rajavithi Medical Center's blood collection room will collect blood samples using a 25-OH Vitamin D reagent kit to measure 25-hydroxyvitamin D through a quantitative chemiluminescent microparticle immunoassay (CMIA). Vitamin D deficiency is defined as levels below 20 ng/mL[11], with severe deficiency classified as below 10 ng/mL and mild to moderate deficiency ranging from 10 to 24 ng/mL[12].

A pelvic ultrasound was conducted in the ultrasound room of the Gynecology Outpatient Department at Rajavithi Hospital by 5 gynecologic staff using a Voluson S6 machine from GE Healthcare Support Services. The procedure involved transvaginal, transrectal, or transabdominal ultrasound methods. For fibroids larger than 10 cm, we used transabdominal ultrasound. For patients with no history of sexual intercourse, we used a transrectal ultrasound. The size of the uterine fibroid was calculated using the formula width × length × height × 0.523, summing the volumes of all fibroids present. There are various types depending on the location, classified according to Fédération Internationale de Gynécologie et d'Obstétrique (FIGO)[13].

Statistical analysis was performed using SPSS for Windows (version 26.0, SPSS Inc., IBM New York, USA). Descriptive statistics for basic demographic data that was categorical was reported as frequencies and percentages. For continuous data, if the data was normally distributed, it was reported as the mean and standard deviation. If the data was not normally distributed, it was reported as the median, minimum, and maximum. The significance level for all tests was set at a p value of less than 0.05. Pearson's correlation was used to assess the relationship between vitamin D levels and fibroid volume. Univariate logistic regression was applied with a significance threshold of 0.2, followed by multivariate analysis with a significance level of 0.05.

Results

The study enrolled a total of 90 patients from July to September 2024. The demographic characteristics of patients in this study are shown

in Table 1. The study involved patients with an average age of 42.2 ± 5.5 years and a mean BMI of 25.2 ± 5.2 kg/m^2. Most patients (66.7%) were nulliparous. The majority (75.6%) had no family history of uterine fibroids. Further details are summarized in Table 1.

Table 1. Baseline characteristics of the patients.

Characteristics	
Age (years), mean ± SD	42.2 ± 5.5
BMI (kg/m^2), mean ± SD	25.2 ± 5.2
Smoking, n (%)	6 (6.7)
Parity, n (%)	
0	60 (66.7)
1-2	25 (27.8)
3-4	4 (4.4)
More than 4	1 (1.1)
Pregnancy interval, n (%)	
Nulliparity	61 (67.8)
1-5 years	1 (1.1)
5-10 years	2 (2.2)
> 10 years	26 (28.9)
Family history, n (%)	
No family history	68 (75.6)
Have family history of uterine fibroid	22 (24.4)
Treatment, n (%)	
Not receiving medication	62 (68.9)
Combined oral contraception	6 (6.7)
Progestin only oral contraception	3 (3.3)
Injectable contraception	16 (17.8)
Intrauterine device	2 (2.2)
Implantation	1 (1.1)
Total myoma volume (cm^3), median (min, max)	24.57 (1.1,1946)

Data were presented as mean ± SD, median (max, min) and number (%).
SD: standard deviation, BMI: body mass index

As shown in Table 2, factors associated with vitamin D levels were assessed. Patients had an average of 1.1 ± 1.2 hours of sun exposure per day, with 74.4% reporting the use of sunscreen. The majority (75.6%) wore short sleeves, and nearly all (94.4%) worked indoors.

Table 2. Factor associated to vitamin D level.

Sun exposure (hours), mean ± SD	1.1 ± 1.2
Sunscreen application, n (%)	67 (74.4)
Cloth, n (%)	
- Wearing long sleeves	22 (24.4)
- Wearing short sleeves	68 (75.6)
Working, n (%)	
- Indoor work	85 (94.4)
- Outdoor work	5 (5.6)
Consuming fish, n (%)	
- Less than 3 times/week	66 (73.4)
- 3-5 times/week	22 (24.4)
- Eating every day	2 (2.2)
Consuming egg, n (%)	
- Less than 3 times/week	40 (44.4)
- 3-5 times/week	34 (37.8)
- Eating every day	16 (17.8)
Drinking milk, n (%)	
- Less than 3 times/week	63 (70)
- 3-5 times/week	10 (11.1)
- Eating every day	17 (18.9)

Data were presented as mean ± SD and number (%)
SD: standard deviation

Serum vitamin D levels of participants are shown in Table 3. The median serum vitamin D level was 20.35 ng/mL (range: 7.5-46), with 48.9% of participants classified as vitamin D deficient.

Table 3. Vitamin D level result (n = 90).

Vitamin D level (ng/ml), median (min, max)	20.35 (7.5, 46)
Vitamin D deficiency, n (%)	44 (48.9)
Severity, n (%)	
- Mild-Moderate	42 (46.7)
- Severe	2 (2.2)

Data were presented as median (min, max) and number (%).

Several factors demonstrate an inverse relationship between vitamin D levels and uterine myoma volume. The baseline characteristics that may influence myoma volume are summarized in Table 4. Among the studied factors, the logarithm of total vitamin D levels showed a significant association with total myoma volume in both univariate and multivariate analyses. In the multivariate model, the coefficient was -1.25, with a p value of 0.026, indicating a statistically significant relationship. Specifically, the odds ratio (OR) for log total vitamin D levels was 0.29 (95% CI 0.09–0.86), signifying a notable decrease in myoma volume with higher vitamin D levels.

Age, however, did not demonstrate a statistically significant effect on myoma volume (p = 0.342). On the other hand, multivariate analysis revealed that higher BMI was associated with larger fibroid volumes, with an OR of 1.04 (95% CI 1.00–1.07). Parity also played a significant role, as having more than three pregnancies

(compared to nulliparity), with an OR of 0.36 (95% CI 0.18–0.73).

Regarding contraceptive use, combined oral contraceptives and injectable contraceptives were significantly associated with smaller fibroid volumes. In both univariate and multivariate analyses, combined oral contraceptives, progestin-only oral contraceptives, and injectable contraceptives showed statistically significant reductions in myoma volume, with odds ratios of 0.48, 0.36, and 0.43, respectively.

Factors associated with vitamin D levels, such as smoking, sun exposure, clothing, sunscreen use, type of work, and diet, were not found to have statistically significant effects.

Table 4. Factor that may influence the logarithm of total myoma volume.

	Univariate		Multivariate		Odds ratio (95% CI)	p value
	95% CI	p value	95% CI	p value		
Interesting factor						
Log total vitamin D	-0.24, -0.18	0.023	-2.35, -0.15	0.026*	0.29 (0.09, 0.86)	0.026*
Baseline characteristic						
Age	-0.05, 0.01	0.149	-0.05, 0.02	0.342	0.98 (0.95, 1.02)	0.342
BMI	-0.01, 0.05	0.191	0.001, 0.07	0.026*	1.04 (1.00, 1.07)	0.026*
Parity						
- Nulliparity	Ref.		Ref.			
- 1-2	-0.68, 0.08	0.122	-0.60, 0.16	0.246	0.80 (0.55, 1.17)	0.246
- > 3	-1.43, 1.85	0.068	-1.73, -0.32	0.005*	0.36 (0.18, 0.73)	0.005*
Treatment						
- No medication	Ref.		Ref.			
- Combined oral contraception	-1.43, -0.10	0.019	-1.37, -0.11	0.023*	0.48 (0.25, 0.90)	0.023*
- Progestin only oral contraception	-1.95, 0.16	0.022	-1.87, -0.15	0.023*	0.36 (0.15, 0.86)	0.023*
- Injectable contraception	-1.13, -0.20	0.001	-1.25, -0.43	< .001*	0.43 (0.29, 0.65)	0.001*
- Intrauterine device	-1.37, 0.80	0.604	-1.59, 0.61	0.385	0.61 (0.20, 1.84)	0.385
- Implantation	-1.65, 1.39	0.869	-1.48, 1.46	0.993	0.99 (0.23, 4.30)	0.993
Factor associated vitamin D level						
Smoking	-0.32, 1.05	0.297			1.44 (0.73, 2.86)	0.297
Sun exposure	-0.04, 1.05	0.161	-0.06, 0.22	0.236	1.66 (0.96, 2.86)	0.161
Cloth	-0.07, 0.71	0.107	-0.58, 0.71	0.094	1.38 (0.93, 2.03)	0.107
Sunscreen application	-0.18, 0.60	0.285			1.23 (0.83, 1.82)	0.285
Working	-0.69, 0.80	0.878			1.06 (0.50, 2.23)	0.878
Consuming fish						
- Less than 3 times/week	-0.95, 0.33	0.342			0.73 (0.39, 1.39)	0.342
- 3-5 times/week	-0.61, 0.78	0.807			1.09 (0.54, 2.18)	0.807
- Eating every day	-.136, 1.22	0.92			1.72 (0.87, 3.39)	0.920
Consuming egg						
- Less than 3 times/week	-0.70, 1.67	0.422			1.62 (0.50, 5.31)	0.422
- 3-5 times/week	-0.91, 1.47	0.642			1.32 (0.40, 4.35)	0.642
- Eating every day	-1.36, 1.22	0.691			0.93 (0.26, 3.39)	0.691
Drinking milk						
- Less than 3 times/week	-0.42, 0.57	0.761			1.08 (0.66, 1.77)	0.761
- 3-5 times/week	-0.60, 0.76	0.823			1.08 (0.55, 2.14)	0.823
- Eating every day	-0.33, 0.85	0.383			1.30 (0.72, 2.34)	0.383

Data were analyzed using univariate and multivariate logistic regression analysis, with a p value threshold of 0.2 in a univariate analysis and a p value threshold of 0.05 in the multivariate analysis.
Coeff: Coefficient, SE: standard error, SD: standard deviation
*significant level

Fig. 1 presents the correlation between the log total myoma volume and the log total vitamin D level. There was a significant inverse correlation between the log total myoma volume and the log vitamin D level among Thai women (Pearson correlation coefficient, r = -0.239; p = 0.023).

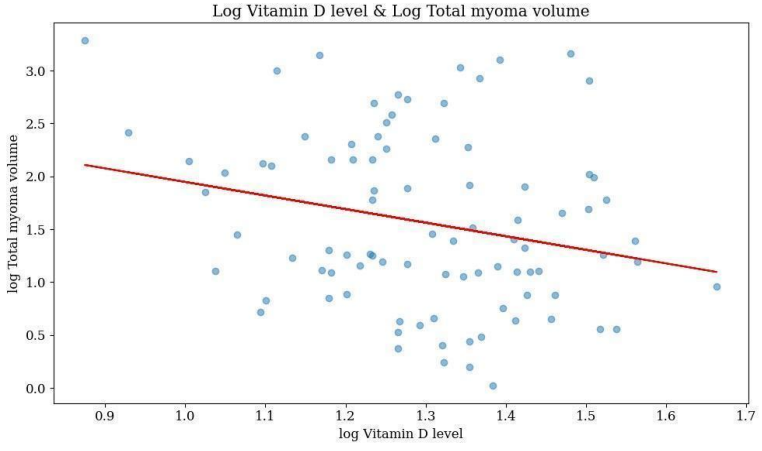

Fig. 1. Correlation between log total myoma volume and log vitamin D level.

Discussion

This study aimed to explore the relationship between uterine fibroid volume and vitamin D levels in Thai women, and we found that serum vitamin D levels were weakly and inversely correlated with uterine myoma volume among Thai women (Pearson correlation coefficient, r = -0.239; p = 0.023). This indicated that lower vitamin D levels were weakly associated with larger total myoma volumes. This finding was consistent with previous studies. For instance, a correlation study by Sarbhai (2021) in India, which reported a Pearson correlation coefficient of -0.292 between vitamin D levels and fibroid volume[10]. Similarly, Srivastava et al (2020)[14] found that lower vitamin D levels were associated with larger fibroid sizes, with a statistically significant difference (p = 0.014). In 2019, Singh also observes that as uterine fibroid volume increased, vitamin D levels significantly decreased (p < 0.044)[15].

The baseline characteristics, such as BMI, also showed a significant positive correlation with myoma volume. Interestingly, parity, particularly having more than 3 children, was associated with a reduced myoma volume.

Other factors associated with total uterine myoma volume included the use of combined oral contraceptives (coeff = -0.778, p = 0.019), progestin-only oral contraceptives (coeff = -1.051, p = 0.022), and injectable contraceptives (coeff = -0.702, p = 0.001). However, these findings differ from previous studies where combined oral contraceptives did not show any reduction in uterine myoma volume[16]. Earlier research has demonstrated a decrease in uterine myoma volume with progestin-only contraceptives, particularly dienogest[17].

Contrary to expectations, lifestyle factors such as sun exposure, sunscreen use, and diet did not significantly impact vitamin D levels in this cohort. This suggested that other factors, such as genetic predisposition or underlying health conditions, may play a more significant role in determining vitamin D levels in women with myoma uteri.

The prevalence of vitamin D deficiency among Thai women with uterine myomas was found to be 48.9%. Singh (2019) also identified vitamin D deficiency as a potential risk factor for myoma

development (p = 0.044), noting that larger myomas were associated with lower vitamin D levels[15]. A systematic review and meta-analysis that examined nine studies found that patients with uterine fibroids had significantly lower vitamin D levels than those without fibroids (p < 0.001). These findings highlighted the potential for exploring vitamin D supplementation as a non-invasive intervention to manage myoma growth.

The strengths of this study included its focus on Thai women, making the findings locally relevant. Additionally, by analyzing multiple factors (e.g., contraceptive use, sun exposure, and diet), the study offers a comprehensive view of influences on myoma volume, potentially guiding future treatment strategies.

However, the study had several limitations. Being a single center study, the result of this study may not represent all Thai women. Also, the accuracy of ultrasound measurements is operator-dependent, although our investigators measurements were standardized, it may still introduce minor errors in evaluating myoma volume. The small sample size may limit the statistical power to detect more subtle correlations. Finally, the lack of longitudinal follow-up prevents the study from assessing how changes in vitamin D levels or treatments may affect the growth or regression of myomas over time.

Lastly, the result of our study probably affirmed that vitamin D level was weak and inversely correlated to the fibroid volume. As uterine fibroids are very common and clearly hold negative impacts on women's quality of life, further study with more comprehensive designs and randomized-controlled trials about the use of vitamin D supplements as a choice of treatment for myoma volume reduction could be beneficial in this field of knowledge.

Conclusion

Serum vitamin D levels were weak and inversely correlated to the myoma uteri volume among Thai women. Further longitudinal and interventional research to determine whether vitamin D supplementation can be a viable strategy for managing fibroid growth are advocated.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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