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Assessment of the Effectiveness of Vitamin D in Reducing Uterine Leiomyoma Size

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ABSTRACT

Abstract: Background: Numerous studies propose vitamin D (VD) as a safe, cost-effective, and non-invasive therapeutic option for uterine leiomyoma (UL), exhibiting antitumor properties with minimal risk of adverse effects. **Objectieve:** This study aimed to assess the effect of vitamin D supplementation (VDS) on the mean diameter of ULs in women with at least one UL >10 mm in size. **Methods:** a randomized, blinded clinical trial included 50 Egyptian women aged 20–50 years with VD insufficiency (serum levels 21–29 ng/mL). Participants were randomly assigned to an intervention group receiving 50000 IU of VD weekly for 8 weeks or a control group receiving no VSD. Comprehensive clinical assessments, including transvaginal ultrasounds and laboratory measurements of serum VD levels, were conducted at baseline and post-intervention. **Results:** The study found no significant differences in baseline demographic characteristics, including age (mean ±SD: study group 35.31 ±7.63 years vs. control group 36.24 ±6.87 years, $p = 0.653$) and body mass index (BMI) (study group 26.17 ±3.72 kg/m² vs. control group 26.86 ±4.31 kg/m², $p = 0.547$). Baseline VD levels were also comparable (study group 22.41 ±3.32 ng/mL vs. control group 22.28 ±3.51 ng/mL, $p = 0.8935$). Post-treatment, VD levels significantly increased in the study group (26.11 ±3.53 ng/mL vs. control group 21.52 ±3.68 ng/mL, $p < 0.0001$). UL diameters showed significant reduction in the study group (35.06 ±10.13 mm) compared to an increase in the control group (45.21 ±13.52 mm, $p = 0.0042$), demonstrating the therapeutic potential of VSD. **Results:** VSD significantly increased serum VD levels and reduced UL diameters in women with UL, highlighting its potential as an effective, non-invasive therapeutic option.

Keywords: leiomyoma, fibroid, vitamin D, vitamin D supplementation, antitumor

1. Introduction

Uterine leiomyoma (UL) is among the most common benign tumors affecting women of reproductive age, with a prevalence ranging from 25% to 80%. Several risk factors are associated with the development of UL, including age, race, body mass index (BMI), hypertension, infertility, and a family history of the condition. Additionally, dietary factors, such as the consumption of soy-based products and food additives, have been suggested to contribute to UL development. The hormonal dependency of UL is underscored by their higher prevalence in women with hyperestrogenic states (Ali *et al.,* 2019; Matyjaszek-Matuszek *et al.,* 2015). UL can alter the responsiveness of myometrial receptors to estrogen, potentially leading to ischemic and epigenetic changes within the leiomyoma tissue (Langà *et al.,* 2017; Yang *et al.,* 2017).

The presence of UL can significantly impair uterine function, manifesting as abnormal uterine bleeding, which often results in anemia due to excessive blood loss. Other symptoms and complications include pelvic pain, dyspareunia, urinary retention or incontinence, and bowel dysfunction (Zimmermann *et al.,* 2012). Additionally, UL may negatively impact reproductive health, contributing

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to infertility, recurrent pregnancy loss, pregnancy complications, preterm labor, and adverse pregnancy outcomes (Guo *et al.,* 2022).

The management of symptomatic UL primarily involves surgical interventions, ranging from myomectomy to hysterectomy, both of which significantly increase healthcare costs. Alarmingly, leiomyomas are reported as the leading indication for hysterectomy in the United States, accounting for one-third to half of such surgeries (Stewart *et al.,* 2016). While non-surgical options exist, their long-term use is often limited due to side effects. Nonetheless, several medical treatments, including levonorgestrel-releasing intrauterine systems (LNG-IUS), gonadotropin-releasing hormone (GnRH) agonists and antagonists, selective progesterone receptor modulators (SPRMs), green tea extracts, and vitamin D (VD), have demonstrated effectiveness in suppressing leimyoma growth. These options are particularly valuable for women seeking fertility preservation (Davari *et al.,* 2021).

Recent research has increasingly focused on VD as a promising, cost-effective, and safe non-surgical treatment for ULs. VD has demonstrated an antitumor effect without significant side effects at therapeutic doses, making it a compelling candidate for UL management (Parazzini *et al.,* 2015).

At the molecular level, VD modulates the expression of genes involved in cell growth, division, proliferation, and differentiation. It has been shown to regulate the expression of genes encoding estrogen and progesterone receptors, induce apoptosis, suppress malignant cell transformation, and inhibit tumor cell proliferation (Ciebiera *et al.,* 2018; Ali *et al.,* 2019; Davari *et al.,* 2021). Additionally, 1α, 25-dihydroxyvitamin D3 [1,25(OH)2D3] exhibits inhibitory effects on melanoma as well as lung, colon, prostate, and breast cancers (Halder *et al.,* 2013; Protic *et al.,* 2016). These properties suggest that VD may play a preventative role in reducing UL risk, particularly in high-risk populations (Bourdet *et al.,* 2015).

Given the widespread prevalence of VD deficiency in Egypt, this study emphasizes the importance of vitamin D supplementation as an accessible and affordable strategy for the prevention and treatment of uterine fibroids.

This study aimed to evaluate the effect of Vitamin D supplementation (VDS) on the mean diameter of UL in women presenting with at least one UL exceeding 10 mm in diameter.

2. Material and Methods

2.1. Study Design

This study was randomized blinded clinical trial included 50 women, and was conducted in accordance with ethical guidelines. Ethical approval was obtained from the Ethics Committee at the Faculty of Physical Therapy [No. P.T.REC/012/003594]. The study adhered to the principles of the Declaration of Helsinki for human research. Written informed consent was obtained from all participants before inclusion.

2.2. Study Population

A sample of 50 Egyptian women was recruited for the study between February 2022 and November 2022.

2.3. Inclusion Criteria

Eligible participants were women aged between 20 and 50 years, all of whom were diagnosed with at least one UL greater than 10 mm in diameter, confirmed via transvaginal ultrasound. All participants exhibited VD insufficiency, as indicated by serum 25-hydroxyvitamin D levels ranging from (21 - 29 ng/ml). The classification of VD levels followed the Endocrine Society Clinical Practice Guidelines, which define sufficiency as (30–100 ng/mL), insufficiency as (21–29 ng/mL), and deficiency as levels below (20 ng/mL; Holick *et al.,* 2011). None of the participants had a history of diabetes, hypertension, or other medical conditions, ensuring a relatively homogeneous study cohort.

2.4. Study Groups

The 50 participants were randomly allocated into two equal groups:

- **Intervention Group :** Comprised 25 women with VD insufficiency, who received 50000 IU of VDS orally once a week for 8 weeks.
- **Control Group:** Comprised 25 women with vitamin D insufficiency who did not receive any VDS.

2.5. Exclusion Criteria

The study excluded women younger than 20 years or older than 50 years. Pregnant women, women with BMI exceeding 35 kg/m², and those with malignancies were also excluded. Participants with a history of diabetes, hypertension, or other medical conditions were not considered. Additionally, women with VD deficiency (serum levels <20 ng/mL) were excluded due to ethical concerns.

2.6. Clinical and Laboratory Assessment

All participants underwent comprehensive clinical evaluation, including general physical examination, abdominal examination, and per vaginal (PV) examination. Transvaginal ultrasound was performed at baseline and after 8 weeks of VDS to measure UL diameter. Diagnosis of UL was based on ultrasound criteria, such as a well-defined, hypoechoic, heterogeneous mass. The ultrasounds were conducted by an experienced radiologist specializing in gynecological imaging who was blinded to group allocation.

Laboratory assessment of serum VD levels was conducted at two time points: baseline and 8 weeks. Blood samples were analyzed in the same laboratory to ensure consistency.

2.7. Statistical Analysis

Statistical analyses were performed using SPSS version 24.0 (IBM, New York, USA). Quantitative data were presented as mean ±standard deviation, while categorical variables were expressed as frequencies and percentages. Data distribution was assessed using the Kolmogorov-Smirnov test. Relationships between variables were analyzed using independent-samples t-tests, one-sample t-tests, and chi-square tests for categorical variables. A p-value of <0.05 was considered statistically significant.

3. Results

This randomized, blinded clinical trial included 50 women diagnosed with at least one UL exceeding 10 mm in diameter, as confirmed by transvaginal ultrasound, and presenting with insufficient VD levels (21–29 ng/mL). Participants were evenly divided into two groups: an intervention group consisting of 25 women who received VDS for 8 weeks, and a control group of 25 women who did not receive any VDS.

3.1. Demographic Characteristics

The demographic data of participants in this study showed no statistically significant differences between the two groups (Table 1). The mean age of participants in the intervention group was 35.31 ± 7.63 years, while that of the control group was 36.24 ±6.87 years. The difference in mean age between the two groups was 0.93 years, with a standard error (SE) of 2.053. The 95% confidence interval (CI) ranged from 3.20 to 5.06. The statistical analysis revealed no significant difference between the two groups (t = 0.453, p = 0.653), indicating that age distribution was comparable across both groups. The mean BMI was 26.17 ±3.72 kg/m² in the intervention group and 26.86 ±4.31 kg/m² in the control group. The difference of 0.69 kg/m² (SE = 1.139) had a 95% CI of 1.60 to 2.98. The results showed no statistically significant difference between the groups (t = 0.606, p = 0.547), suggesting that BMI was similarly distributed in both groups.

Table 1: Demographic Data

Variable	Intervention Group (Mean ± SD)	Control Group (Mean ± SD)	Difference	SE	CI	DF	t	P
Age (years)	35.31 ± 7.63	36.24 ± 6.87	0.93	2.053	3.20 to 5.06	48	0.453	0.653
BMI (kg/m²)	26.17 ± 3.72	26.86 ± 4.31	0.69	1.139	1.60 to 2.98	48	0.606	0.547

3.2. Vitamin D Level Before and After Treatment:

Before the intervention, the mean VD levels were 22.41 ±3.32 ng/mL in the intervention group and 22.28 ±3.51 ng/mL in the control group. The difference was minimal (-0.13 ng/mL, SE = 0.966), with a 95% CI of 1.81 to 2.07. Statistical analysis showed no significant difference (t = 0.135, p = 0.8935), confirming that baseline Vitamin D levels were comparable between the groups (Table 2).

Following the VDS, the intervention group showed a marked increase in mean VD levels (26.11 ±3.53 ng/mL), compared to the control group (21.52 ±3.68 ng/mL). The mean difference was 4.59 ng/mL (SE = 1.020), with a 95% CI of 2.54 to 6.64. The results were statistically significant (t = 4.501, p < 0.0001), indicating the effectiveness of VDS in the intervention group (Table 2).

Table 2: Vitamin D Levels Before and After Vitamin D Supplementation

Variable	Intervention Group (Mean ± SD)	Control Group (Mean ± SD)	Difference	SE	CI	DF	t	P
Vit D level before ttt (ng/ml)	22.41 ± 3.32	22.28 ± 3.51	0.13	0.966	1.81 to 2.07	48	0.135	0.8935
Vit D level after ttt (ng/ml)	26.11 ± 3.53	21.52 ± 3.68	-4.590	1.020	2.54 to 6.64	48	4.501	< 0.0001

3.3. Leiomyoma Diameter Before and After Treatment between the Two Groups

The initial UL diameters were 42.55 ±13.27 mm in the intervention group and 42.03 ±13.56 mm in the control group. The difference of 0.52 mm (SE = 3.80) had a 95% CI of 7.11 to 8.15. No significant difference was observed between the two groups (t = 0.137, p = 0.8916), indicating similar baseline UL diameters (Table 3).

After eight weeks of treatment, the intervention group demonstrated a significant reduction in mean UL diameter (35.06 ±10.13 mm) compared to the control group (45.21 ±13.52 mm). The mean difference was 10.155 mm (SE = 3.379), with a 95% CI of 3.36 to 16.94. This difference was statistically significant (t = 3.004, p = 0.0042), suggesting that VDS effectively reduced UL size in the intervention group (Table 3); (Figure 1).

Drawing from the previous analysis, VDS resulted in a significant increase in VD levels and a reduction in UL diameters in the intervention group, highlighting its potential therapeutic benefit.

Table 3: Leiomyoma Diameter Before and After Vitamin D Supplementation

Variable	Intervention Group (Mean ± SD)	Control Group (Mean ± SD)	Difference	SE	CI	DF	t	P
Leiomyoma diameter before ttt (mm)	42.55 ± 13.27	42.03 ± 13.56	0.520	3.80	7.11 to 8.15	48	0.137	0.8916
Leiomyoma diameter after ttt (mm)	35.06 ± 10.13	45.21 ± 13.52	10.155	3.379	3.36 to 16.94	48	3.004	0.0042

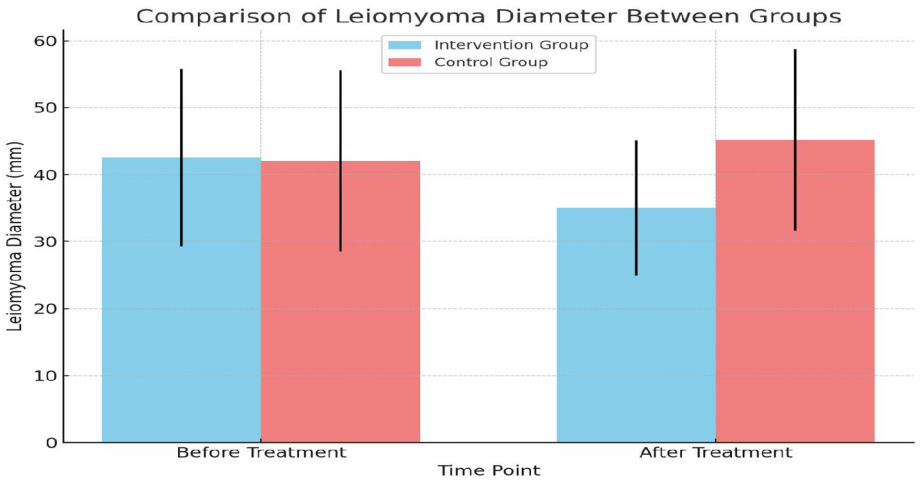

Fig. 1: Leiomyoma Diametr Before and After Vitamin D Supplementation.

Interestingly, we analyzed and compared the UL diameters measured before and after the 8-week treatment period within each group to quantify the observed changes, to evaluate the effect of VDS on Leiomyoma size (Table 4). After treatment, the intervention group showed a significant reduction in mean UL diameter to 35.06 ±10.13 mm (mean reduction: 7.49 mm, SE = 3.339, CI: 0.78 to 14.20, DF = 48, t = 2.243, p = 0.0295), while the control group exhibited a non-significant increase to 45.21 ± 13.52 mm (mean increase: 3.18 mm, SE = 3.830, CI: 4.52 to 10.88, DF = 48, t = 0.830, p = 0.4105). Subsequently, these findings suggest a significant therapeutic effect of VDS on UL size and its beneficial therapeutic effect.

Table 4: Leiomyoma Diameters within each group

Group	Leiomyoma diameter before ttt (mm)	Leiomyoma diameter after ttt (mm)	Difference	SE	CI	DF	t	P
Intervention Group n = 25	42.55 ± 13.27	35.06 ± 10.13	7.49	3.339	0.78 to 14.20	48	2.243	0.0295
Control Group n = 25	42.03 ± 13.56	45.21 ± 13.52	3.180	3.830	4.52 to 10.88	48	0.830	0.4105

4. Discussion

Vitamin D, primarily in its biologically significant form vitamin D3 (VD3), plays a crucial role in human health, serving as a marker of total VD activity (Ciebiera *et al.,* 2018). It exhibits antiproliferative properties and promotes tumor necrosis factor release, exerting cytotoxic effects on tumor cells (Lips, 2006). Studies suggest VD deficiency may increase the risk of UL (Baird *et al.,* 2013; Sabry *et al.,* 2013; Ciebiera *et al.,* 2016), with evidence from animal models indicating that high doses can reduce UL size (Al-Hendy and Badr, 2014; Ali *et al.,* 2020). However, its exact role in UL pathogenesis and treatment requires further investigation.

This randomized, blinded clinical trial assessed the effects of VDS on UL in 50 women with leiomyoma diameters ≥10 mm and VD insufficiency. Participants were randomized into an intervention group (received VDS) and a control group (no VDS). Baseline characteristics, including age, BMI, serum VD levels, and UL diameters, were comparable between groups. After 8 weeks, the intervention group showed a significant increase in VD levels (26.11 ±3.53 ng/mL vs. 21.52 ±3.68 ng/mL, $p < 0.0001$) and a reduction in UL diameter (35.06 ±10.13 mm vs. 45.21 ±13.52 mm, $p = 0.0042$), while the control group exhibited no significant changes, suggesting VD's potential efficacy in UL management.

Our findings align with a randomized, blinded trial by Davari *et al*. (2021), which assessed the impact of VDS on UL growth. This study, involving 204 women with insufficient VD levels (20–30

ng/mL) and ULs ≥10 mm, reported a significant increase in serum VD levels in the intervention group (28.56 ng/mL) vs. (22.72 ng/mL) in the control, $p < 0.05$). In the intervention group, the average UL diameter before and after 8 weeks of VDS was (43 ±4.68 mm) and (42.6 ±1.31 mm), respectively. In contrast, the control group, which did not receive VDS, had an average UL diameter of (41.98 ±5.25 mm) before VDS and (47.81 ±3.42 mm) after 8 weeks. The difference in the mean UL size between the groups, showing a 5.83 mm increase in the control group and a 0.48 mm decrease in the intervention group, was statistically significant ($P<0.001$). Their conclusion support the efficacy of VD in preventing UL growth.

Rosen *et al*. (2018) reported an 85% prevalence of VD deficiency in women with UL compared to 8% in the general American population, suggesting VD deficiency as a risk factor for UL development. Similarly, Oskovi *et al*. (2017) observed significantly lower serum 25-hydroxyvitamin D levels in Turkish women with UL compared to controls (6.54 ±4.66 ng/mL vs. 8.18 ±5.16 ng/mL; $p = 0.009$). These studies underscore the potential of VD deficiency as a modifiable risk factor for UL.

Preclinical studies further corroborate these findings. Brakta *et al*. (2015) demonstrated that VD3 inhibits leiomyoma cell proliferation in vitro and reduces tumor growth in vivo, positioning it as a promising non-surgical treatment option for ULs. Similarly, Guo *et al*. (2022) employed a two-sample Mendelian randomization approach, confirming a causal relationship between elevated serum VD levels and reduced UL risk.

Conversely, Mitro and Zota (2015) conducted a cross-sectional analysis involving 3,590 women and found no association between serum VD levels and UL prevalence. However, subgroup analysis revealed that insufficient VD levels were significantly associated with higher odds of ULs in white women, though not in Black women. They attributed these discrepancies to potential methodological limitations.

Back to our study, we observed a significant impact of VDS on the growth reduction of UL. Based on our findings, we propose that VD may exert a beneficial antitumor effect on UL development. The strengths of our study include its randomized, blinded design and rigorous inclusion and exclusion criteria. However, the short follow-up period (8 weeks) limits the generalizability of the findings. Future studies with longer follow-up periods are recommended to evaluate the sustained effects of VDS.

Conclusion

Our study demonstrated that VDS significantly reduces UL size in women with VD insufficiency, highlighting its potential as a safe, cost-effective, and non-invasive treatment option for ULs. These findings, supported by prior clinical and preclinical studies, emphasize the need for further research to explore the long-term benefits of VD in managing UL.

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Conflict of interest

All authors have no conflict of interest.

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Author contribution

Kareem El-Nahhas: (corresponding author): Design of work, manuscript writing, data collection, clinical and ultrasound assessment; **Mahmoud Zaatar:** Research idea, data collection, clinical and ultrasound assessment; **Safenaz Y. El Sherity:** Anthropometric evaluation, ultrasound assessment; **Maya G. Aly:** Anthropometric evaluation. All the authors have read and approved the final version of the manuscript. **Kareem El-Nahhas**, had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

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