Original Article

Effect of Two Different Doses of Vitamin D Supplementation on Uterine Myoma on South East Iranian Population: A Clinical Trial

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Abstract

Objective: Uterine myoma is the most common benign tumor however with significant distress and reduced quality of life in affected women. Besides, vitamin D deficiency may be a risk factor for uterine myoma. This study aimed to evaluate the effect of vitamin D supplements on the size of myoma in women with vitamin D insufficiency or deficiency.

Materials and methods: This clinical trial was conducted in a teaching hospital from 2019 to 2020. According to baseline vitamin D level, participants were assigned into two interventional equal groups (vitamin D deficiency or insufficiency) to receive either 1000 IU daily or 50000 IU weekly vitamin D for 12 weeks. The size and location of the uterine myoma were compared before and after the intervention.

Results: Totally, 137 women with uterine myoma were enrolled. Based on baseline vitamin D level, 52 cases had vitamin D insufficiency and 85 cases had vitamin D deficiency. No significant difference was observed in age and BMI in both groups. The location of the subserosal and intramural myoma did not differ, otherwise, the percent of the submucosal myomas were increased significantly (p=0.020) after the intervention. In both groups decreased myoma size otherwise not significant was seen after the intervention (p=0.148 and p=0.664 respectively).

Conclusion: Vitamin D supplementation may not be effective in women with vitamin D insufficiency or deficiency in the short term to reduce myoma size.

Keywords: Uterine; Vitamin D; Fibroid

Introduction

The most common benign tumors in women are uterine myomas which originate from the smooth muscles of the uterus and are estrogen dependent (1). The exact causes of myoma formation are unclear while genetics, hormonal status, and growth factors have been considered to play roles (2, 3). Near 50%

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of myoma are symptomatic and present with pelvic pain, hemorrhage, and complaints of the urinary system based on the size, location and number of myoma (4, 5). Uterine myoma symptoms negatively impact physical and social life and may decrease health-related quality of life and productivity (6). Most myomas require surgery when symptomatic. Although finding the nonsurgical treatment methods are mandatory (7).

Vitamin D which is known as calcium-phosphorus hemostasis regulator is known to have an immunomodulatory role. 1, 25-dihydroxycholecalciferol, the active form of the hormone is cell proliferation and angiogenesis modulation (8-10). The active form of vitamin D regulates genes of cell cycles which will result in a decrease in cell proliferation (11).

Literature shows that hypovitaminosis D results in an increased risk of uterine myoma (12-14). In vitro studies demonstrated that vitamin D supplements prevent the growth of myoma cells and promote the apoptosis of cells (15). There is little evidence about the effect of vitamin D supplements on uterine myoma size, so we designed this study to assess the effect of vitamin D supplements on the size of uterine myoma in women with vitamin D deficiency or insufficiency.

Materials and methods

Study setting: This clinical trial was conducted in Amiralamomenin hospital (a teaching hospital affiliated to Zabol University of Medical Sciences) between March 2018 and January 2019.

Ethical consideration: All cases were asked to complete informed consent forms before study entrance. The study had been approved by the ethics committee of Zabol University of Medical Sciences with reference number: ZBMU.1.REC.1396.66.

Inclusion and exclusion criteria: Inclusion criteria were the women aged 35 to 45 years with a history of single myoma (all types) and also serum vitamin level ≤30 nanograms/milliliter who desired to participate in the study. All vitamin D measurements were performed in a single laboratory. The exclusion criteria were any past metabolic disease, multiple myomas and using any hormonal or anti-hormonal drug for therapy. Indeed the patients with a past or current history of any cancer or premature ovarian failure were excluded either. All participants were from a parallel sociodemographic level with similar diet intake.

Patient's allocation: Patients initially underwent ultrasound to examine myoma and their serum levels of vitamin D were assessed. Indeed, body mass index (BMI), myoma characteristics and age were collected. According to baseline vitamin D level, patients were assigned into two groups. In the deficiency group ((vitamin D deficiency (< 20 nanograms/milliliter)) pearl vitamin D 50000 IU (Zahravi Company) every week for 12 weeks was administered. In insufficiency group (vitamin D insufficiency (20-30 nanograms/milliliter)) pearl vitamin D 1000 IU (Zahravi Company) every day for 12 weeks were used. Nor the patients nor the physicians were blinded to the groups of patients. Before and after the intervention, pelvic ultrasound was done by an expert radiologist and the size of the uterine myoma and location (intramural, submucosal or subserousal) were recorded. Serum vitamin D level after the intervention was assessed by intravenous blood sampling.

Statistical analysis: Data analysis was performed by SPSS version 22 (SPSS Inc., Chicago, IL, USA). Data were presented as Mean±SD for continuous or frequencies for categorical variables. Continuous variables were compared using independent sample t-test and categorical variables compared with the chi-squared test. A *P*-value less than 0.05 was considered significant.

Results

Totally 137 women with uterine myoma were enrolled. Based on baseline vitamin D level, 52 cases had vitamin D insufficiency and 85 cases had vitamin D deficiency. Demographic data and the level of vitamin D before and after intervention are presented in Table 1. The demographic characteristics had no a significant difference between groups. The vitamin D level in both groups was improved after 12 weeks of therapy with significantly differences (p=0.033).

Table 1: Demographic data and the level of vitamin D before and after intervention

Variables (mean±SD)	Vitamin D insufficiency (n=52)	Vitamin D deficiency (n=85)	p
Age (year)	41.2±6.5	39.4±6.6	0.232
BMI (kg/m^2)	25.7±2.4	25.6±2.9	0.160
Baseline vitamin D	24.8±2.8	12.2±3.8	<0.001
Final vitamin D level	37.6±10.0	32.7±10.2	0.033

BMI: body mass index

The most common site of myoma in both groups was intramural. The location of the subserosal and intramural myoma did not differ, otherwise, the percent of the submucosal myomas were increased significantly (p=0.024) after intervention (Table 2).

Table 2: comparison the myoma location before and after intervention

Myoma Location n (%)	Before intervention	After intervention	p
Subserosal	26 (50%)	40 (47.1%)	0.738
Intramural	30 (57.6%)	59 (69.4%)	0.163
Submucosal	0	8 (9.4%)	0.024

n: number

The initial size of myoma in the deficiency group was significantly higher than in the insufficiency group (P=0.012). This trend was repeated after intervention either (P=0.013). However, in the insufficiency group, there was a 3.8% decrease in myoma size after intervention which was not statistically significant (P=0.148). Otherwise, in the deficiency group, there was a 2.4% reduction in myoma size, which was not statistically significant (P=0.664) either.

Discussion

The result of the current study showed that vitamin D supplements (even 1000 IU or 50000 IU) did not affect the size of myoma in Iranian women with vitamin insufficiency or deficiency. In vitro studies demonstrated that vitamin D supplements could downregulate the proliferating of cell nuclear antigen (PCNA), cyclin-dependent kinase 1, and B-cell lymphoma 2 which will result in uterine myoma growth prevention (15).

Also, a review study about the role of vitamin D in the treatment of uterine myoma showed that vitamin D significantly (both in vivo and in vitro) reduces the proliferation of myoma cells and their growth, so vitamin D can be an effective and safe treatment and alternative to a variety of surgical methods (16).

In a previous study, Ciavattini et al. reported a negative correlation between vitamin D level and volume of the myoma. They treated one group of women with myoma with vitamin D supplements and the other were controls. They found that the size and volume of the myoma increased in the control group significantly while the diameter of the myoma did not change significantly in the intervention group (17). They also reported a negative correlation between vitamin D level and the size of the myoma. In our study, the initial size of the myoma deficiency group was larger than the insufficiency group that may be indicated that vitamin D deficiency may be a trigger for myoma. However, due to many confounding factors, the results are not easily generalizable.

In 2013, a study was conducted on 154 premenopausal women with normal uterine or at least one myoma that showed the low level of vitamin D was significantly associated with the prevalence of myoma and it was also observed that women with lower levels of vitamin D had a larger myoma size (18).

On the other hand, another study showed that vitamin D supplements may reduce the size of the myoma in women with vitamin D deficiency compared with controls (19). This is not in line with our study. Maybe because we did not have a control group and the size and type of the myoma were not specified in that study.

One of the limitations of this study was the short follow-up period of patients**.** Longer follow-up with larger sample size may be predicting more accurately the effect of vitamin D on myoma growth. Considering the different results in various studies, suggesting that the relation between vitamin D and myoma is still a challenging issue, so to clarify it conducting clinical trials with control group is recommended.

Conclusion

Vitamin D supplementation may not be effective in women with vitamin D insufficiency or deficiency in the short term to reduce the myoma size.

Conflict of Interests

Authors have no conflict of interests.

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References

1. Cheng MH, Wang PH. Uterine myoma: a condition amendable to medical therapy? Expert Opin Emerg Drugs 2008; 13: 119-33.
2. Flake GP, Andersen J, Dixon D. Etiology and pathogenesis of uterine leiomyomas: a review. Environ Health Perspect 2003; 111: 1037-54.
3. Arslan AA, Gold LI, Mittal K, Suen T-C, Belitskaya-Levy I, Tang M-S *et al.* Gene expression studies provide clues to the pathogenesis of uterine

leiomyoma: new evidence and a systematic review. Human reproduction 2005; 20: 852-63.
4. Buttram Jr VC, Reiter RC. Uterine leiomyomata: etiology, symptomatology, and management. Fertil Steril 1981; 36: 433-45.
5. Niroomand N, Hajiha S, Tabrizi NM, Ghajarzadeh M. A single dose of misoprostol for reducing hemorrhage during myomectomy: a randomized clinical trial. Arch Gynecol Obstet 2015; 292: 155-8.
6. Ghant MS, Sengoba KS, Recht H, Cameron KA, Lawson AK, Marsh EE. Beyond the physical: a qualitative assessment of the burden of symptomatic uterine fibroids on women's emotional and psychosocial health. J Psychosom Res 2015; 78: 499-503.
7. Farris M, Bastianelli C, Rosato E, Brosens I, Benagiano G. Uterine fibroids: an update on current and emerging medical treatment options. Ther Clin Risk Manag 2019; 15: 157-78.
8. Schwartz GG, Wang M-H, Zang M, Singh RK, Siegal GP. 1 alpha, 25-Dihydroxyvitamin D (calcitriol) inhibits the invasiveness of human prostate cancer cells. Cancer Epidemiology and Prevention Biomarkers 1997; 6: 727-32.
9. Lokeshwar BL, Schwartz GG, Selzer MG, Burnstein KL, Zhuang SH, Block NL ,*et al.* Inhibition of prostate cancer metastasis in vivo: a comparison of 1, 25-dihydroxyvitamin D (calcitriol) and EB1089. Cancer Epidemiol Biomarkers Prev 1999; 8: 241-8.
10. Mantell DJ, Owens PE, Bundred NJ, Mawer EB, Canfield AE. 1α, 25-dihydroxyvitamin D3 inhibits angiogenesis in vitro and in vivo. Circ Res 2000; 87: 214-20.
11. Bläuer M, Rovio PH, Ylikomi T, Heinonen PK. Vitamin D inhibits myometrial and leiomyoma cell proliferation in vitro. Fertil Steril 2009; 91: 1919-25.
12. Al-Hendy A, Badr M. Can vitamin D reduce the risk of uterine fibroids? Womens Health (Lond Engl) 2014; 10: 353-8.
13. Brakta S, Diamond JS, Al-Hendy A, Diamond MP, Halder SK. Role of vitamin D in uterine fibroid biology. Fertil Steril 2015; 104: 698-706.
14. Paffoni A, Somigliana E, Vigano' P, Benaglia L, Cardellicchio L, Pagliardini L, *et al.* Vitamin D status in women with uterine leiomyomas. J Clin Endocrinol Metab 2013; 98: E1374-8.
15. Sharan C, Halder SK, Thota C, Jaleel T, Nair S, Al-Hendy A. Vitamin D inhibits proliferation of human uterine leiomyoma cells via catechol-O-methyltransferase. Fertil Steril 2011; 95: 247-53.
16. Brakta S, Diamond JS, Al-Hendy A, Diamond MP, Halder SK. Role of vitamin D in uterine fibroid biology. Fertil Steril 2015; 104: 698-706.
17. Ciavattini A, Delli Carpini G, Serri M, Vignini A, Sabbatinelli J, Tozzi A *et al.* Hypovitaminosis D and "small burden" uterine fibroids: Opportunity for a vitamin D supplementation. Medicine (Baltimore) 2016; 95: e5698.
18. Downes E, Sikirica V, Gilabert-Estelles J, Bolge SC, Dodd SL, Maroulis C, *et al.* The burden of uterine fibroids in five European countries. Eur J Obstet Gynecol Reprod Biol 2010; 152: 96-102.
19. 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 J Intern Med 2019; 10: 125-31.

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