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Vitamin D Deficiency May Be a Modifiable Risk Factor in Women With Endometriosis

Marzieh Derakhshan[1,2], Maryam Derakhshan[3*], Pegah Hedayat[3], Maryam Shiasi[1], Erfan Sadeghi[4]

Abstract

Objectives: This study aimed to determine the levels of 25(OH) D in endometriosis patients and to clarify the association between the endometriosis and dietary intake of calcium and vitamin D.

Materials and Methods: A total of 200 women with endometriosis as endometriosis group and 154 healthy women (control group) of reproductive age were included in this study. The plasma 25(OH) D (vitamin D3) level was measured by high-pressure liquid chromatography method in endometriosis and control (healthy) groups. Participants in these 2 groups were asked about the dietary intake of calcium and vitamin D.

Results: Our result showed the association between 25(OH) D deficiency and endometriosis risk (odds ratio [OR] = 29.4, $P<0.001$). The intake of dietary calcium was also inversely associated with recurrence of endometriosis. However, this association was not observed between vitamin D intake and endometriosis.

Conclusions: Our results showed that the decreased level of vitamin D (VD) is associated with the endometriosis risk. Accordingly, the authors validate that vitamin D deficiency may be regarded as a predisposing factor for endometriosis. In addition, a decreased risk of endometriosis with increasing calcium (Ca) intake was observed. Therefore, using Ca as dietary supplementation may be useful in the management of endometriosis in patients.

Keywords: Vitamin D deficiency, Endometriosis, Calcium intake

Introduction

Endometriosis, one of the most common gynecological diseases, is an estrogen-dependent, chronic painful inflammatory disorder. It is related to infertility and is characterized by the presence of endometrial-like tissue outside the uterine cavity. Based on retrograde theory, endometrial tissues implant in ectopic site of endometrium, especially in the peritoneal cavity or ovary during menstruation. According to metaplasia theory, endometriosis may also have malignant potential (1).

Some studies highlighted the role of inflammation-related mediators in the control and treatment of endometriosis considering the important impact of the immune-mediated inflammatory pathway in the pathogenesis of this disorder (2).

Vitamin D (VD) is a pleiotropic molecule with a broad range of biological activities such as mineralization of the skeleton and regulation of plasma calcium levels, and modulation of the immune system (3,4). Recent investigations emphasized the antiproliferative, anti-inflammatory and anti-invasive effects of 25(OH) D on cancer cells (5).

VD deficiency is prevalent in some populations (6). Low level of 25(OH) D is a predisposing and risk factor for some diseases, including diabetes, cancers, breast cancer, preeclampsia, recurrent pregnancy losses (RPL) and autoimmune diseases such as rheumatoid arthritis, multiple sclerosis (6-9). Endometriosis risk may also be affected by the low concentration of VD (10).

Vitamin D receptor (VDR) has been expressed in many human tissues, also in cycling endometrium, proposing a role in the regulation of normal cellular growth and inhibition of cell proliferation in a variety of cancer cells through modulation of the expression of growth factor receptors and induction of apoptosis (11). Immunomodulatory responses of 1,25-dihydroxy vitamin D3 (1,25(OH)2D3), a biologically active form of VD, have been shown to affect the control of endometriosis through cytokine production which decrease pro-inflammatory and increase anti-inflammatory factors. In addition, recent findings have shown that VD could also induce apoptosis within the endometriotic lesions (12-14).

Diet (dairy foods) is an affecting factor in the emergence and progression of endometriosis. Recent studies have suggested that dietary calcium may reduce the inflammatory stress (15).

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[1]Department of Anatomy, Tehran University of Medical Sciences, Tehran, Iran. [2]Gynecology and Andrology Center, Khanevadeh Hospital, Esfahan, Iran. [3]Department of Pathology, Isfahan University of Medical Sciences, Isfahan, Iran. [4]Department of Biostatistics and Epidemiology, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran
*Corresponding Author: Maryam Derakhshan, MD; Tel: +983136688597, Email: m_derakhshan58@yahoo.com

Few studies have assessed the association between 25(OH) D levels and endometriosis (15-17). The results of the mentioned studies were contradictory. Two aforementioned studies[16,17] found a positive association between 25(OH) D levels and endometriosis, but, Harris et al in 2013 observed a lower percentage of endometriosis among women with elevated levels of serum 1,25-dihydroxy VD (15). As endometriosis risk may be affected by the level of VD and diet, the authors aimed to clarify the association between endometriosis and 25(OH) D levels. Moreover, it was assessed whether the intake of calcium (Ca) and VD were associated with endometriosis.

Materials and Methods

Patient Population

A retrospective cohort study was performed at Alzahra hospital, Isfahan, Iran. A total of 200 women with laparoscopically confirmed ovarian endometriosis (as endometriosis group) and 154 healthy women (as control group) of reproductive age were included in this study. Therefore, participants were divided into groups including endometriosis and control groups that were examined in terms of serum 25(OH) D (vitamin D3) levels through blood sample and a comprehensive questionnaire on the infertility status, parity, Ca and VD intake. Women with endometriosis referred to the Gynecological Surgical Service for laparoscopy between April 2014 and June 2016. Endometriosis was staged according to the revised American Society for Reproductive Medicine (ASRM) classification. All the cases included in the study were patients who typically had stage III to IV ovarian endometriosis. The stages of endometriosis are characterized using the location, extent and depth of endometrial implants, size and adhesion of endometrioma. There were chocolate cysts at the third stage of endometriosis. A large number of cysts and severe adhesions were seen in four stages of endometriosis (18). Patients with diabetes, menopause, malignancy, hypertension, renal diseases, and hormonal treatment were excluded.

The mean age of the patient and control group was 31.21 ± 7.1 and 30.6 ± 7.52, respectively. The mean body mass index (BMI) of the patient and control group was 22.1 ± 3.2 and 22.06 ± 3.8, respectively.

Blood Sample

Blood samples were obtained from all patients before laparoscopy in the endometriosis group and healthy woman without any history of endometriosis as the control group. To avoid confounding factors, they were asked to avoid taking VD supplement before the test. The participants in the control group were volunteers who were recruited from the general population.

The quantitative determination of serum 25(OH) D (vitamin D3) was performed in 2 groups by our standardized routine procedure based on the high-pressure liquid chromatography (HPLC method). The reference ranges for 25(OH) D were classified as 1-10 ng/ml, 10-30 ng/mL, 30-100 ng/mL which were defined as the deficiency, insufficiency and normal ranges of 25(OH) D, respectively (19). These aforementioned levels were also classified based on ethnics and population condition in our country.

After blood sampling, all women in endometriosis and control (healthy) groups received a comprehensive questionnaire on the infertility status, parity, Ca and VD intake. Using the Women's Health Initiative Food Frequency Questionnaire, participants were asked about their intake of Ca and VD.

Regarding the intake of Ca, participants of 2 groups were asked about the frequency of their dietary Ca intake, either dietary sources or dietary combined with supplementation sources. Their intake of Ca was considered in the form of never or less than once a day or 2 or more times a day. Regarding the intake of VD, participants were only asked about supplementation sources of it. Their intake of VD was classified as never to once or more times a month.

Although the season of blood sampling and the fraction of the ethnicity are considered as 2 factors which can affect the level of VD, these factors were similarly ignored in both groups.

Statistical Analysis

SPSS version 20.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. To evaluate the associations between the disease status (endometriosis) and risk factors, a multiple logistic regression using the Enter method was performed, taking disease status as the binary response variable. Independent variables and the estimated coefficients, odds ratios and corresponding confidence intervals are given in tables. Results were considered statistically significant when $P<0.05$.

Results

A total of 200 women with endometriosis (endometriosis group) as well as 154 healthy women (control group) were studied for this evaluation. The prevalence of infertility in endometriosis and control groups was 41.7% and 16.8%, respectively. Marriage status in endometriosis and control group was 77.9% and 77.1%, respectively (Table 1). Parity in endometriosis and control group was 41.7 and 1.8, respectively.

Of all cases in endometriosis group, the numbers of the cases with 25(OH) D deficiency, 25(OH) D insufficiency and normal 25(OH) D were reported to be 112 (57.7), 45 (23.2), 37 (19.1) patients, respectively. In control group, aforementioned levels of 25(OH) D were 34 (22.1), 54 (36.4), 64 (41.6), respectively (Figure 1). The prevalence of endometriosis in the cases with vitamin D3 levels lower than normal was 80.9 % and 58.4% in endometriosis and control group, respectively.

Table 1. Characteristics of the Endometriosis and Control Groups

Factor	Control Group	Endometriosis Group
	Vitamin D Level	
Deficient	34 (22.1)	112 (57.7)
Insufficient	56 (36.4)	45 (23.2)
Normal	64 (41.6)	37 (19.1)
Infertile	21 (16.8)	70 (41.7)
Marriage	111 (77.1)	148 (77.9)
Child	53 (62.4)	67 (65.7)
Vitamin D intake	65 (45.8)	58 (32.6)
Ca intake	77 (56.2)	46 (26.7)

Values are represented as Number (Percent).

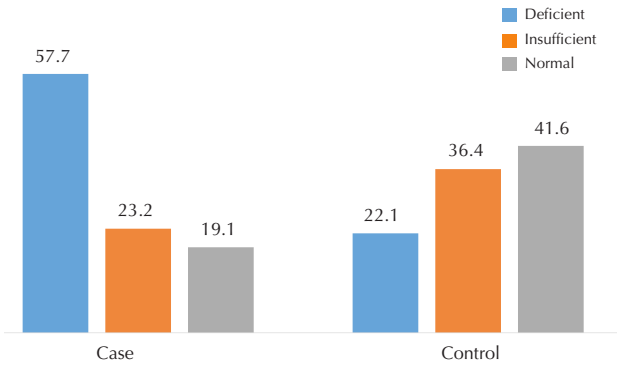

Figure 1. The Frequency of 25(OH) D Deficiency, 25(OH) D Insufficiency and Normal 25(OH) D in Endometriosis (Case) and Control Groups.

The regression analysis confirmed the significant association between 25(OH) D level and endometriosis when comparing 2 groups. Accordingly, in the endometriosis group, the overall rate of 25(OH) D deficiency was significantly higher compared to control group (odds ratio [OR] = 29.4, $P < 0.001$). Moreover, the prevalence of 25(OH) D insufficiency in patients was significantly higher compared to the control group (OR = 15. 6, $P < 0.01$). According to the regression analysis, the odds of endometriosis are almost 30 times and 16 times higher in women with VD deficiency and those with VD insufficiency respectively, which is statistically significant.

Intakes of calcium were significantly associated with lower risk of endometriosis with a multi-variable adjusted rate ratio of 0.297 (95% CI: 0.123, 0.719; $P = 0.007$). However, the intake of Vitamin D as supplements was not associated with endometriosis (OR = 1.571, $P = 0.312$) (Table 2). CA intake and marriage also seem to decrease the odds of endometriosis by 70 and 94%, respectively. Other factors do not seem to have a significant association with endometriosis.

There was also a significant association between the marriage and infertility and the prevalence of endometriosis. Accordingly, infertile and married women are at more risk of having endometriosis compared to the healthy and unmarried ones (OR = 6 for infertile status). However, no association was found between the age and parity in the women with and without endometriosis (OR = 0.9, 2.05 respectively) (Table 2).

Discussion

Endometriosis, which affected 6% to 10% of women of reproductive age, has many criteria for the autoimmune diseases and mimics malignancy (20,21). Although the current medical treatment of endometriosis including conventional surgical approaches, hormonal drugs and antioxidants have been proposed in this disorder, these are not yet satisfactory. Considering that the immune and chronic inflammatory responses have been suggested as a part of endometriosis pathogenesis, recent evidence emphasized the immune modularly role of VD. It is necessary to assess VD supplement in the management of endometriosis.

In our study, women with laparoscopically diagnosed endometrioma have significantly lower 25-OH VD levels as compared with that of normal controls (OR = 29.4, $P < 0.001$). Our findings are in line with a large prospective study showing that the greater predicted plasma 25(OH) D levels are associated with a lower risk of endometriosis. It was conducted over a 14-year period and included 1385 patients with endometriosis. Harris et al in 2016, showed that women with high VD level had 24% lower risk of endometriosis than those with low VD level (RR = 0.76, $P_{trend} = 0.004$) (15).

Table 2. Multiple Logistic Regression Models with Endometriosis as the Response Variable

	Beta	SE	OR	95% CI for OR	
				Lower	Upper
Age	-0.009	0.029	0.991	0.937	1.049
Marriage	-2.817	1.107	0.060*	0.007	0.523
Parity	0.719	0.526	2.052	0.732	5.754
Infertility	1.777	0.610	5.910**	1.789	19.524
Vitamin D deficiency	3.383	0.710	29.461***	7.321	118.552
Vitamin D insufficiency	2.749	0.805	15.624**	3.225	75.691
Vitamin D intake	-1.213	0.446	1.571	0.655	3.766
Ca intake	3.383	0.451	0.297**	0.123	0.719

* Significant at 0.05,** Significant at 0.01,***Significant at 0.001.

In our earlier study, the authors showed the involvement of the immune system in the pathogenesis of endometriosis (22). Delbandi et al in 2016 demonstrated the modulatory role of VD including invasion and pro-inflammatory cytokine production, promotion of cell adhesion and inhibition of proliferation of endometriotic stromal cells (ESCs) in endometriosis patients (11). In this regard, Miyashita et al also showed the anti-inflammatory effect of VD in ESCs through the reduced IL-1Beta or TNF alfa-induced IL-8 mRNA expression (10).

In another study, the anti-proliferative effects of VD on cell growth control in endometrial carcinoma were determined. It was found that VD may protect the progression of endometrial carcinoma by activating CYP27A1 and CYP2R1 pathway (23). In another study, although VD reduced DNA synthesis, it did not induce apoptosis in ESCs (10). Our data were not supportive of a relationship between level (grade) of endometriosis and level of VD. It would be best if the relationship between VD and endometriosis grading was examined to predict the possible role of VD in the progression of endometriosis.

A decreased risk of endometriosis with increasing Ca intake was observed. These results are in accordance with the study of the mouse model and it was shown that the intake of milk reduced the production of tumor necrosis factor α and interleukin-6. These factors involved in the inflammatory pathway and oxidative stress (24). However, in 2 prospective studies, no significant association between the milk or cheese intake and endometriosis risk was reported (25,26). Moreover, the main part of our data is in line with the recent report showing that either the intake of dairy Ca or plasma level of VD is inversely associated with endometriosis (15). However, the significant association between VD intake and lower risk of endometriosis was not observed. It seems that the numbers of our participants are not sufficient for VD supplementation trial.

In addition, our findings indicate that endometriosis affects infertility risk. Endometriosis is considered an estrogen-dependent disease associated with dysmenorrhea, irregular uterine bleeding and infertility (27). On the other hand, the association between the level of VD and pregnancy rate was also assessed. The finding demonstrated that VD deficiency is associated with lower pregnancy rates (7,28).

Finally, our results showed that the decreased level of VD is associated with the endometriosis risk. Based on the results found, the authors confirm that VD deficiency may be regarded as a predisposing factor for endometriosis. A decreased risk of endometriosis with increasing Ca intake was also observed. Therefore, using Ca as dairy supplementation may be useful in the management of endometriosis in patients.

Conflict of Interests

Authors have no conflict of interests.

Ethical Issues

This study was approved by the Ethics Committee of Isfahan University of Medical Sciences, Isfahan, Iran (2014/391374). Informed consent was obtained from all the participants before inclusion in the study.

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