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Is there an association between serum vitamin D levels and endometrial polyps?

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Summary

Background/Aim: Anti-proliferative effects of vitamin D (VD) had been proposed previously. Herein, the authors aimed to evaluate serum 25(OH)VitD3 levels in women with endometrial polyps (EPs) and to determine whether VD deficiency is a risk factor for EP formation. *Materials and Methods:* This study was designed as a controlled cross-sectional study. Forty three women with polyps constituted the study group whereas 47 of them constituted the control group. The selection criteria for the study group were hysteroscopic detection and histological confirmation of EPs. The main parameters recorded for each woman were; age, body mass index (BMI), parity, smoking status, co-morbidities, dressing style, dairy intake of VD-rich foods, duration of sunlight exposure, skin photo-type, serum levels of 25(OH)VitD3, calcium, phosphor, and albumin. *Results:* The mean serum 25(OH)VitD3 level was 8.3±7.7 ng/ml in the study group and 9.3 ± 10.2 ng/ml in the control group ($p = 0.583$). Mean BMI was statistically significantly higher in the study group ($p = 0.003$). Logistic regression model showed that only significant risk factor for EPs was increased BMI (OR=1.241; 95% CI = 1.070-2.440; $p = 0.004$). *Conclusion:* VD deficiency is common among the reproductive age women and obesity is the most important risk factor for polyp formation. The authors believe that there is no relation between VD and EPs.

Key words: Endometrial polyps; Risk factors; Vitamin D.

Introduction

Endometrial polyps (EPs) are one of the most common benign gynecologic disorders. A true polyp is defined as a localized overgrowth of the endometrial glands and stroma through the uterine cavity, with an incidence of 25% and reported to be a cause of abnormal uterine bleeding in peri menopausal women [1-3]. The exact etiopathology of this condition is still unclear. However, it is known that estrogen and progesterone regulate endometrial proliferation and differentiation, and EPs have both estrogen and progesterone receptors that may play a key role in the etiopathogenesis [4]. The well-known risk factors for polyps are hormonal factors, obesity, late menopause, hormone replacement therapy, polycystic ovary syndrome (PCOS), and tamoxifen use [5].

Vitamin D (VD) is primarily involved in metabolism of calcium-phosphorus and regulates bone mineralization. It is a fat soluble vitamin and provides intestinal absorption of calcium by increasing VD dependent calcium binding proteins. It is generally accepted that VD functions as a steroid hormone, since the vitamin D receptor (VDR) is considered a member of the nuclear receptor super family [6]. The main source of VD is sunlight induced synthesis in the skin, and subsequently it is biologically activated by a variety of enzymatic reactions. A small amount of circulating VD is supplied by diet or food supplements. VD deficiency is associated with increased risk of malignancies, diabetes, cardio-vascular disease, infectious, neuromusculoskeletal, and autoimmune disorders [7].

It has been shown that VD plays an important role in cell proliferation, differentiation, and immune responsiveness. Many in vitro and in vivo studies demonstrate dose-dependent effects of VD analogs on cell proliferation and differentiation. In addition, it was speculated that VD deficiency and low calcium intake may contribute to the development of endometrial cancer [8]. In a previous study, authors suggested that genetic variants of an enzyme involved in active VD metabolism may contribute to its antiproliferative effects among the endometrial cells [9].

In this study, the authors aimed to evaluate serum 25(OH)VitD_3 (biologically *active form of VD*) levels in women with EPs and to determine whether VD is a risk factor for the development of EPs showing sometimes abnormal proliferative patterns.

Materials and Methods

Ninety women who applied to the gynecology and infertility clinics of the Zekai Tahir Burak Women's Health Education and Research Hospital between September 2014 and November 2014 were included in this cross-sectional, case controlled study. The study was approved by the institutional ethical review board and informed consent was obtained from all participants. The study

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group included 43 women with polyps, and the control group included 47 women without polyps. The selection criteria for the study group were hysteroscopic detection and histological confirmation of EPs. The inclusion criteria for the control group were absence of endometrial pathology in hysteroscopic observation and absence of endometrial hyperplasia, endometrial carcinoma, and EPs in hysteroscopic and histological evaluation. Patients with thyroid disorders, PCOS rheumatological or adrenal diseases, hepatic or renal failure, diabetes, and hypertension were excluded from the study. Current VD and VD containing multivitamin users, and steroids users were also excluded from the study. The risk factors recorded for each patient were age, body mass index (BMI), parity, abortion, smoking status, educational level, co-morbidities, dressing style, dairy intake of VD-rich foods, duration of sunlight exposure, skin photo-type, monthly income, serum levels of 25(OH)VitD_3, calcium, phosphor, and albumin.

The study was carried out during the autumn period in Ankara (Longitude: 40° 4' N, Latitude: 32° 34' E, Altitude: 891 m), and the average temperature was 7-18.7 °C. Ankara has a continental climate which refers cool, snowy winters and hot, dry summers due to its elevation and inland location. Rainfall occurs mostly during the spring and autumn. The weather was rainy about six days of each month during the study period, and also six hours per day it was sunny during the study period [10].

After following at least eight hours of fasting, venous blood samples were drawn from each participant and were poured into the gel tubes, and they were transferred to the laboratory in a light-proof box not to be exposed to light. After clotting, tubes were centrifuged at 4,100 × g for ten minutes, and each serum was separated and immediately analyzed for VD and other biochemical markers. Serum levels of 25(OH)VitD_3 were measured by using an ELISA Kit. All blood samples were analyzed at the biochemistry laboratory of the present hospital. The intra-assay and inter-assay coefficients of variation were 8.9% and 10.6% for serum 25(OH)VitD_3.

Covered dressing style was defined as covering head and arms but not hands and face with clothes, while the uncovered dressing style was defined as head and arms uncovered. Dietary intake of VD-rich foods was evaluated according to scientific recommendations. An intake of three cups of dairy products, five ounces meat or equivalent protein, and four cups of vegetables such as mushroom per day for all women was regarded as sufficient consumption of these foods. The consumption of three ounces of fish twice a week and at least four medium-sized eggs with yolks per week were also considered adequate. The consumption of the aforementioned foods lesser than the specified values was regarded as insufficient consumption [11]. Skin photo types were classified into six types, according to Fitzpatrick's classification (type 1 being the lightest and type 6 the darkest) [12]. The level of physical activity was determined according to the weekly activity reported by the patients. The level of activity was classified as moderate with either of the following criteria: three or more days of vigorous activity of at least 20 minutes per day, five or more days of moderate-intensity activity and/or walking of at least 30 minutes per day, five or more days of any combination of walking, and moderate-intensity or vigorous intensity activities achieving a minimum of at least 600 MET-minutes/week. If any one of the following two criteria was present, it was regarded as high activity; vigorous-intensity activity on at least three days and accumulating at least 1,500 MET-minutes/week, seven or more days of any combination of walking, moderate-, or vigorous-intensity activities accumulating at least 3,000 MET-minutes/week [13]. Anthropometric data were collected by the physician on the same day of blood taken. Height and weight of the patients were measured using a professional calibrated device. Body mass index (BMI) was calculated as weight in kilograms divided by height per meters squared (kg/m^2)Transvaginal ultrasonography was performed on all of the women following a complete pelvic examination. Patients with a suspicious finding on ultrasound, such as endometrial thickening, underwent office hysteroscopy (HS). All office procedures were performed on an outpatient basis during the early follicular phase of the menstrual cycle, without the use of a tenaculum or anesthesia. Office HS was performed with a five-mm, 30° rod lens, and continuous-flow mechanical office hysteroscope. All patients diagnosed with polyps underwent an operative HS (the same brand) procedure performed under general anesthesia with a monopolar cutting loop and ten-mm rigid resectoscope. Microscopic specimens were assessed by the authors' pathology department; all were histologically suggestive of EP.

Table 1. — *Comparison of demographic and laboratory parameters between the two groups.*

	Study group (n:43)	Control group (n:47)	*p*
Age (years)	32.3 ± 5.6	30.4 ± 5.7	0.084
Parity	1 (0–6)	0 (0–4)	0.021
Abortion	0 (0–3)	0 (0–9)	0.353
25OHVitD_3 (ng/ml)	8.3 ± 7.7	9.3 ± 10.2	0.583
Calcium (mg/dl)	9.1 ± 0.7	9.1 ± 0.9	0.695
Phosphor (mg/dl)	3.4 ± 0.6	3.2 ± 0.4	0.063
Albumin (mg/ml)	4.3 ± 0.4	4.3 ± 0.4	0.472
Income (TL/monthly)	1827 ± 927	1582 ± 571	0.298
BMI (kg/m^2)	27.6 ± 5.1	24.7 ± 3.8	0.003

BMI: body mass index; TL: Turkish Liras.
Data are as mean ± standard deviation and median (minimum-maximum).
$p < 0.05$ is considered statistically significant.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences version 15.0. Normal distribution of the data was assessed using the Kolmogorov–Smirnov test. Continuous and normally distributed variables were presented as means ± standard deviation, and intergroup differences were investigated using Student's *t*-test. Continuous variables with non-normal distribution were expressed as medians (minimum–maximum), and differences between variables were analyzed using the Mann–Whitney U test. Differences between categorical data were evaluated using the Pearson chi square and Fisher's exact tests where appropriate. Binary logistic regression analysis was used to reveal risk factors for EPs. Pearson correlation analysis adjusted for age was used for assessing the associations between VD and other parameters. Sample size was determined according to the results of the central limit theorem. A *p*-value < 0.05 was considered to indicate significance.

Results

The mean age of the patients in study group was 32.3±5.6 years and in control group 30.4±5.7 years ($p = 0.084$). The mean of BMI was 27.6 ± 5.1 kg/m^2 and 24.7 ± 3.8 kg/m^2 in study and control groups, respectively ($p = 0.003$). Multiparity was more common among women with EPs ($p = 0.021$). There were no statistically significant differences between two groups according to serum levels of calcium,

Table 2. — *Distribution of the parameters that may affect serum vitamin D levels between the groups.*

	Study group (n=43)	Control group (n=47)	*p*
Comorbidity	40/3	43/4	0.811
Previous surgery	24/19	27/20	0.799
Educational level			0.062
Primary	30	25	
High school	13	22	
Profession			0,503
House-wife	35	42	
Official	4	3	
Worker	4	2	
Dressing style			0.564
Covered	18	20	
Uncovered	25	27	
Smoker	31/12	36/11	0.493
Photo type			0.518
Type 1-2	13	10	
Type 3-4	23	31	
Type 5-6	7	6	
Physical activity			0.546
Inactive (< 600 MET)	5	3	
Low (600-3000 MET)	27	34	
Adequate (> 3000 MET)	11	10	
Diary product	36/7	39/8	0.723
Fish	37/6	36/11	0.157
Meat	38/5	38/9	0.199
Eggs	42/1	43/4	0.086
Mushroom	35/7	36/11	0.430
Sunlight exposure			0.659
< 10 min	10	13	
10-20 min	24	23	
> 20 min	9	11	

Data are presented as numbers.

Table 3. — *Logistic regression analysis of risk factors for endometrial polyps.*

	Wald	*p*	OR	95% CI
BMI	8.125	0.004	1.241	1.070−2.440
Age	2.181	0.140	1.067	0.979−1.163
Vitamin D	0.048	0.827	0.994	0.942−1.049
Calcium	0.071	0.790	1.085	0.596−1.973
Comorbidity	0.764	0.382	2.261	0.363−14.072
Previous surgery	0.209	0.647	1.251	0.479−3.266
Multiparity	0.088	0.766	1.158	0.439−3.057
Smoker	1.739	0.187	0.476	0.158−1.435

OR= odds ratio, CI= confidence interval.
$p < 0.05$ is considered statistically significant.

phosphor, albumin, and total protein ($p > 0.05$). The mean serum 25(OH)VitD_3 level were lower in the study group, but it was found to be statistically insignificant (8.3 *vs.* 9.3, $p = 0.583$). Only one woman showed an adequate serum 25(OH)VitD_3 level in both groups. Thirteen (27.7%) patients had severe VD deficiency (≤ five ng/ml), 20 (42.6%) had moderate deficiency (five to ten ng/ml), and 13 (27.7%) had mild deficiency (11-20 ng/ml) in the study group. These numbers in the study group were 16 (37.2%), 13 (30.2%), and 13 (30.2%), respectively. The demographic and laboratory features of the patients are depicted in Table 1. Partial correlation analysis showed that there was a significantly positive correlation between 25(OH)VitD_3, calcium, and phosphor (r = 0.201, $p = 0.047$; r = 0.205, $p = 0.043$, respectively), calcium and phosphor (r = 0.317, $p = 0.001$), and albumin, calcium, and phosphor (r = 0.898, $p < 0.001$; r = 0.260, and $p = 0.010$, respectively).

The number of employees, educational level, comorbidity, and previous history of surgery did not differ between two groups. Also dressing style, smoking status, skin photo type, physical activity, and dietary intake of VD rich foods, which may have affected the serum levels of VD, were statistically insignificant determinants. Previous cesarean operation was the most common cause of surgical history. The patients had no significant comorbidities except an asthma and epilepsy patient without history of drug use. The vast majority of the participants was exposed to sunlight between ten to 20 minutes during the daytime (09:00 a.m. - 03:00 p.m.) (Table 2). Logistic regression method showed that higher BMI was the only significant risk factor for EPs (Odds ratio [OR], 1.241; 95% confidence interval [CI]; 1.070-2.440, $p = 0.004$) (Table 3).

Discussion

In this study, patients with EPs were evaluated for serum levels of 25(OH)VitD_3 and compared with age-matched controls, with the aim of determining whether VD is risk factor for polyp formation. The present results suggest that VD deficiency is common among the reproductive age women, and that obesity is the most important risk factors in the development of EPs, whereas VD was found not to be an independent risk factor for EPs.

EPs caused by the proliferation of endometrial glands and stroma are often benign lesions that contain both estrogen and progesterone receptors [4]. There are limited studies on the pathogenesis of EPs. However, it was shown that prolonged endometrial exposure to mitogenic effects of estrogen, unopposed by progestin, is recognized as a contributor to the various proliferative endometrial disorders [14]. EPs also have high expression of aromatase enzyme activity. Maia *et al.* [15] showed that the presence of aromatase expression was significantly higher in EPs than in normal endometrium. Peripheral aromatase activity is associated with aging and adiposity. Aromatase enzyme activity increases in the presence of obesity and sex hormone-binding globulin (SHBG) decreases; as a result, free estrogen levels increase [16].

It is classically known that insulin is an anabolizing hormone, which plays a crucial role in the cellular prolifera-

tion directly or indirectly via insulin like growth factors (IGF). Obesity also plays an important role in the pathogenesis of insulin resistance that can result in the proliferation of tumor cells. Insulin and IGFs stimulate hormone-dependent cell proliferation, which is demonstrated through the growth of breast and colon cancer. Serhat *et al.* [17] previously reported that obesity is an independent risk factor in the development of EPs. Hypertension and diabetes mellitus were not determined as risk factors associated with EPs. Bakour *et al.* [18] found that age, gravidity, parity, menopause status, and tamoxifen use were risk factors associated with EPs, whereas hormone replacement therapy was not. Dreisler *et al.* [19] suggested that being overweight (BMI > 25kg/m^2) and using hormones in the postmenopausal period are positively correlated with polyps. While the incidence of EPs increases with age, they are more common in premenopausal women than in postmenopausal women. A previous study found the prevalence of EPs to be 12% in premenopausal women and 6% in postmenopausal women [20]. In the present study, the authors firstly excluded these confounder factors such as diabetes, hypertension, and menopause status from the study. Also, mean BMI, which is the quantitative value of body fat and obesity, was significantly higher in the study group. The findings in the current study were similar to results found in the literature and compatible with the literature increased BMI was found to be only significant risk factor for EPs.

VD is essential for the development, growth, and maintenance of healthy bones during lifetime of a human. Besides the osteoblast and the small intestine, the VDR has been identified in almost every tissue and cell in the body, including brain, heart, skin, pancreas, breast, colon, and immune cells [21]. VD also inhibits the cell proliferation and stimulates the differentiation of normal as well as malignant cells [22]. Its anti-neoplastic effects had been shown in various type of cancer, which requires a higher dose to reduce cancer cell proliferation. However, supra-physiologic use of active VD is hampered by its calcemic side effects. Therefore, VD derived analogs were developed that are characterized by lower calcemic side effects and stronger anti-neoplastic effects. Some VD analogs have been approved in the treatment of psoriasis that is a hyperproliferative condition of the skin [23]. There are several publications suggesting that there might be a possible association between nasal and colonic polyps and serum VD levels. A meta-analysis showed that there was a consistent inverse relationship between serum VD levels and colorectal cancer [24]. In the study of Wang *et al.* [25], VD levels were significantly lower in patients with chronic rhinosinusitis with nasal polyps, which revealed an association with greater nasal polyp. In another study authors concluded that women who have low levels of circulating VD may be at higher risk of distal colorectal adenomas [26]. However, the available data are especially conflicting for colonic polyps. Adams *et al.* [27] suggested that the established inverse association between circulating VD and colonic adenoma may not apply to hyperplastic polyps. However, Sy and Bautista [28] pointed out a possible threshold effect of 25(OH)VitD_3 at < 30 ng/ml associated with increasing odds of being colonic polyps.

EPs generally do not lead to serious health problems. They sometimes may cause excessive uterine bleeding, that may consequently cause anemia. The malignant potential of EPs is controversial; but in general, malignant transformation of these lesions is very rare and occurs most commonly in the postmenopausal period. In a previous study, endometrial carcinoma was found in 3.9% of postmenopausal women with an EP [29]. Giordano *et al.* [30] reported that age, menopausal status, hypertension, and obesity may increase the risk of premalignant and malignant polyps. Petterson *et al.* [31] suggested a three-fold increased risk of developing endometrial carcinoma in women who previously underwent endometrial curettage and was diagnosed with an EP. In another previous cohort study, the prevalence of EP was found to be 24% in 1,305 endometrial biopsies, and that there was a 0.06% risk of a premalignant or malignant lesion [32]. Kilicdag *et al.* [33] showed that premenopausal women with PCOS and those with two or more polyps had an increased risk of malignancy. Premalignant or malignant conditions were found in 2.2% of 417 premenopausal women in their study. There were no cases of adenocarcinoma or hyperplasia with atypia confined to EPs diagnosed in the present study. The reason for this may be due to the young age of women.

The vast majority of VD is synthesized in the skin by the sunlight. However, vegetarians, Black race, sedentary life, and women with limited sun exposure as those who live in cold climates and northern latitudes or prefer covered dressing style are under the risk of VD deficiency. The present authors designed a study assessing the factors that may affect serum VD levels. Although 25(OH)VitD_3 levels were lower in the study group, the differences between mean 25(OH)VitD_3 level and associated factors were not statistically significant. In the present study the authors also found that the mean serum level of 25(OH)VitD_3 was very low, but there is no consensus on an optimal serum level to maintain overall health. However, most agree that at least 20 ng/ml serum level is required for bone health [7]. To the present authors' knowledge, this study carried out on this issue is the first clinical study in the literature. Although it was attempted to be a well-designed, cross-sectional in nature study, it may not reveal a clear cause-effect relationship.

In conclusion, according to this study, VD deficiency is common among reproductive-aged women. However, there is no relation between VD deficiency and EPs. The most important risk factor for EP formation seems to increase in BMI. Future large-scale studies are required to evaluate the effects of VD in the development of EPs.

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