Research Article

Surgery and Clinical Practice

Impact of Vitamin D Levels Drop on Endometria Hyperplastic Post-Menopausal Bleeding

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ABSTRACT

Background: *The prevalence of cancer, including endometrial cancer, continues to grow. A prelude to cancer is thickening of the endometrium, one of the formidable signs of neoplasia development can be bleeding. In recent years, there have been reports in the literature on the possible role of vitamin D in the development of endometrial diseases, but the data in some cases have been quite contradictory. In this regard, we examined patients with endometrial hyperplasia who applied to the Oncology Center and Obstetrics and Gynecology Department of Azerbaijan Medical University in 2021-2024 years.*

The study aimed to investigate the relationship between vitamin D levels and the manifestations of hyperplasia and neoplasia, with the goal of developing a comprehensive set of corrective and preventive measures.

Methods: *The patients were stratified into 3 groups: group I - patients with endometrium hyperplasia with bleeding diagnosed with neoplasia, group II - patients with endometrial hyperplasia and bleeding but without neoplasia, group III - patients with endometrial thickening but without bleeding and without oncology.*

The hormonal panel was examined on the IMMULITE 2000 XPI (SIEMENS) analyzer. Test for 25-hydroxy vitamin D (25(OH)D) was conducted on ARCHITECT i1000 SR immunological analyzer (Abbott Park, IL). Study results were interpreted using the SPSS version 26.

Results: *The most significant correlation in vitamin D levels and severity of disease manifestations was observed in the main group, namely endometrial hyperplasia associated with postmenopausal bleeding complicated by cancer.*

Conclusion: *We identified vitamin D deficiency as a risk factor among women with endometrial hyperplasia aggravated by neoplasia.*

Keywords

Vitamin D, Endometrial thickness, Post-menopausal bleeding, Cancer.

Introduction

The increased risk of cancer due to deteriorating living conditions, polluted environment and bad habits has become the scourge of modern times [1]. The incidence of cancer continues to rise. Kotsopoulos J and colleagues report that over an average follow-up period of 6.7 years, 38 new cases of endometrial cancer were diagnosed among carriers of BRCA1 and BRCA2 mutations, with a mean age at diagnosis of 58.4 years [2]. Farhangnia P. and coauthors state that vitamin D deficiency can lead to cancer and reproductive organs disorder [3]. In recent years, the idea has been put forward about the possibility of vitamin D use in the malignant neoplasms treatment, and vitamin D has been considered an anti-

cancer vitamin. Post-analysis analyses of recent mega-trials of extra skeletal effects of vitamin D suggest a link between vitamin D status and the immune system [4]. Immune system suppression of cancer spread is the only mechanism to stop neoplasia development, and Vitamin D strengthens immunity by involvement in leucocytes differentiation [5]. Masood T and colleagues highlight the circadian nature of vitamin D fluctuations, [6] suggesting its involvement in more complex regulatory mechanisms than currently understood.

The endometrium comprises receptors that respond to the in the blood-washed tissue level of estrogen and progesterone, released into the bloodstream via stimulation by pituitary gonadotropins, namely FSH and LH. The receptors respond to hormones even in menopause [7] Yarmolinskaya MI and co-authors report that in endometrioid heterotopias the number of vitamin D receptors VDR AE decreases compared to both proliferative and secretory endometrium of patients with endometriosis, which sheds light on the involvement of vitamin D in the pathogenesis of endometriosis. The authors conclude that it is necessary to prescribe cholecalciferol as a promising therapy for endometrial diseases [8]. There are some reports that administration of vitamin D induce endometrial proliferation in pregnant women [9].

Endometrial hyperplasia is often associated with bleeding, especially in cases of neoplastic transformation. Levin A. and colleagues state that a lower glomerular filtration rate is associated with a reduced level of $1,25(OH)_2D_3$ [10], as the kidneys are responsible for producing the active form of vitamin D. In turn, vitamin D facilitates the reabsorption of calcium (Ca) from primary urine back into the bloodstream. It is well-known that vitamin D plays a crucial role in maintaining the balance of calcium (Ca) and phosphorus (P) levels in the blood, with calcium being essential for coagulation, therefore, a drop in vitamin D levels may serve as a potential predictive marker for bleeding episodes.

Endometrial hyperplasia is also often associated with obesity and insulin resistance [11,12]. For this reason, metformin has been proposed as a therapy for endometrial hyperplasia. Since metformin has a fairly wide range of side effects, we decided to find out vitamin D role in disease etiology, which would allow us to offer a more gentle vitamin D to help improve these patients life quality, because the data on vitamin D impact on endometrial hyperplasia remains inconclusive, highlighting the need for further research to clarify its potential benefits for this condition. This study aimed to assess the effect of reduced blood vitamin D levels on endometrial thickness in patients, especially with neoplasia. A randomized trial was conducted involving 90 postmenopausal women diagnosed with endometrial hyperplasia.

Patients and Method

90 patients were enrolled in the current study. All participants signed an agreement, and the work was approved on protocol No. 20 of Azerbaijan Medical University Ethics Committee.

Inclusion Criteria

Menopause for no less than 12 months, endometrial thickness > 5mm.

Exclusion Criteria

Menopause <12 months, endometrial thickening <5mm.

The patients were categorized into three groups:
Group I - Women with post-menopausal bleeding, whose malignant changes were detected by histopathology analysis.
Group II - Women with endometrial thickness and bleeding but without malignant changes.
Group III - Patients with endometrial thickness without bleeding.

Research Methods

The research work was carried out in 2023-2024 at the Department of Obstetrics and Gynecology of the Azerbaijan Medical University.

The hormonal spectrum of the blood was examined on the IMMULITE 2000 XPI (SIEMENS) analyzer. For this, follicle stimulating hormone (FSH), luteinizing hormone (LH), as well as prolactin and estradiol levels was measured. Malignant degeneration diagnosis was established by patients in the main group and comparison groups' endometrial tissue histological and immunohistochemical examination. For histological examination, a standard method of staining the material with hematoxylin and eosin was used [13]. Test for 25-hydroxy vitamin D (25(OH)D) were performed in venous blood on the ARCHITECT i1000 SR immunological analyzer (Abbott Park, IL). Study results were analyzed using the SPSS version 26 Program for qualitative variables with chi-square test, significance of $P \leq 0.05$.

Results

This study focused on 90 post-menopausal women aged between 52 and 65 years (average age: 58.05 ± 4,37 years). Main group we primarily focused on, covered 25 post-menopausal women experiencing bleeding caused by endometrial hyperplasia with diagnosed cancer (27,5% of all cases endometrial hyperplasia). Comparison group comprised 45 women with endometrial thickening accompanied by bleeding, but without cancer (approximately half of the total examined). The control group comprised 20 women with endometrial thickening without bleeding, making up roughly one-fifth of the total participants.

Analysis of gynecological anamnesis showed that parity 1-2 was in 48,6 ± 5.8% of the examined women, and in the comparison group - 52.73 ± 8.2%, in the control group - 43.0 ± 12.4%, while parity 3-4 was in 13.8 ± 7.3% of patients in the main group, 12,56 ± 3,25 in comparison group and in 5,26 ± 3,34 in III group women. Rest patients were infertile. When analyzing the total number of abortions and births, the significant difference were noted between main and control groups ($p<0.05$).

Comparative analysis of the hormonal panel in the studied groups revealed that the FSH levels raised above 25.8-134.8 mIU/mL and was higher than accepted norm in 48.2 ± 9.8% of women in the main group, in 32.2 ± 7.3% of women in the comparison group, and in the control group this parameter deviates from the norm in 15,02 ± 6.4%. The LH levels raised above 25.8 IU/L and was higher than normal in 32.2 ± 7.5% of women in the main group,

in 31.8 ± 7.2% of women in the comparison group, and in 12,4 ± 4,1% in control group. A decrease in estradiol to and below 16.2 ± 1.7 pg/ml was observed in 45,6 ± 5,8% of women in the main group, in 28,9 ± 8.8% of women in the comparison group. The estradiol level in the control group of women deviate from the norm in 14,7 ± 4,3%. Based on the findings of our USG study, the following distributions of endometrial thickness were observed: in first group, the endometrial thickness ranged between 14–18 mm in 54.13 ± 5.3% of cases, 19–22 mm in 31.22 ± 5.4%, and >23 mm in 14.55 ± 4.8%. In comparison group, the endometrial thickness was 14–18 mm in 84.23 ± 5.4% of women, 19–22 mm in 13.25 ± 3.7%, and 23–29 mm in 2.45 ± 0.2%. In control group, the endometrial thickness was observed at 14–18 mm in 60.22 ± 5.6% of patients, 19–22 mm in 10.21 ± 3.4%, and 23–29 mm in 29.4 ± 7.2%.

Uterine submucosal myoma was detected via ultrasound examination in 42.4 ± 5.6% of patients in the main group, with 13.32 ± 7.1% presenting multiple myomas. In the comparison group, uterine submucosal myoma was identified in 35.10 ± 6.3% of women, with a multiple character observed in 12.4 ± 2.2% of cases. In the control group multiple myomas were found in 6 ± 0,3% cases.

Relation of Vitamin D drop with endometrium thickening

Results examinations showed significant difference in vitamin D levels in groups (P<0.01), Table 1.

Figure 1 shows the average vitamin D drop association with endometrial thickening.

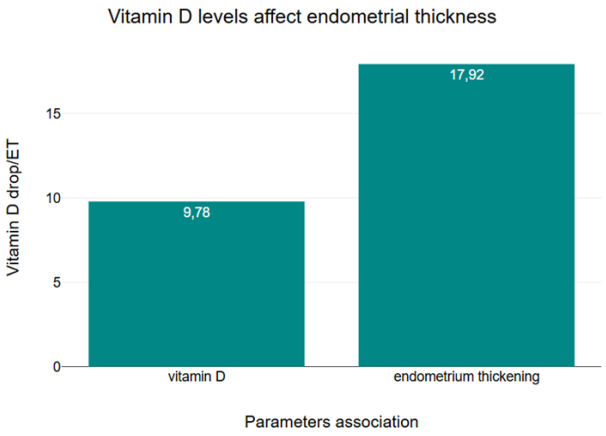

Figure 1: Decrease in vitamin D results in increase of endometrium thickening.

In the first and second groups, where endometrial thickening was most pronounced in the majority of patients, normal levels of 25(OH)D (>30 ng/ml) were not detected. The figure (Figure 2) below illustrates the association between low vitamin D levels in the main group and endometrial thickening.

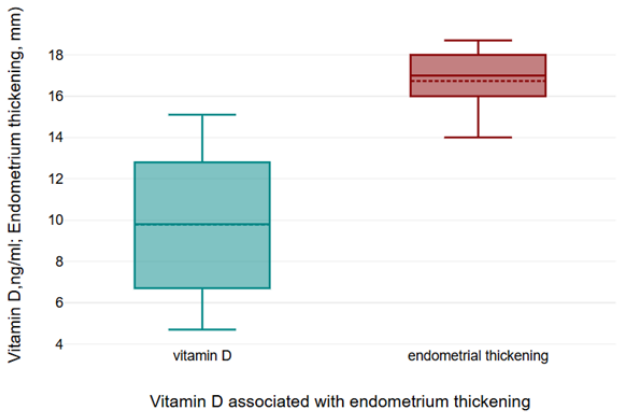

Figure 2: Visualization of increase in endometrial thickness: dependence on vitamin D drop.

Results of the Pearson correlation (Figure 3) indicated that there is a significant large negative relationship between vitamin D and endometrial thickening in main group ($r(42)$ = NaN, p = aN).

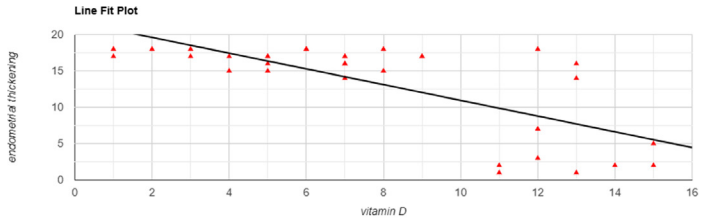

Figure 3: Pearson correlation between vitamin D and endometrial thickening.

Additionally, the dispersion of endometrial thickness and vitamin D levels in the main group demonstrates a significant association between low vitamin D levels and increased endometrial thickness (Figure 4).

Vitamin D deficiency reached 9.78 ± 3.59ng/ml in main group, 12.6 ± 2.7 in comparison group, and in 89,3 ± 12,3% of women in control group vitamin D levels was less than 30 ng/ml, namely 13.87 ± 3.82.

Table 1: Vitamin D levels in patients with cancerous/non-cancerous post-menopausal endomentrial bleeding.

Group	N	Cases of FSH raise (in %)	Cases of LH raise (in %)	Cases of estradiol drop (in %)	Vitamin D (ng/ml)	P-value for vitamin D
Main group (bleeding +cancer)	25	48.2 ± 9.8 P<0.001*	32.2 ± 7.5 P>0.05*	45,6 ± 5,8 P<0.001*	9.78 ± 3.59	P<0,01*
Comparison group (bleeding without cancer)	45	32.2 ± 7.3 P<0.001**	31.8 ± 7.2 P<0.001**	28,9 ± 8.8 P<0.001**	12.6 ± 2.7	<0,001**
Control group	20	15.02 ± 6.4	12.4 ± 4,1	14.7 ± 4.3	21.87 ± 3.82	

Note: *N represents the number of patients. In the main group, *indicate comparisons with the II group, while **reflects differences relative to the control group.*

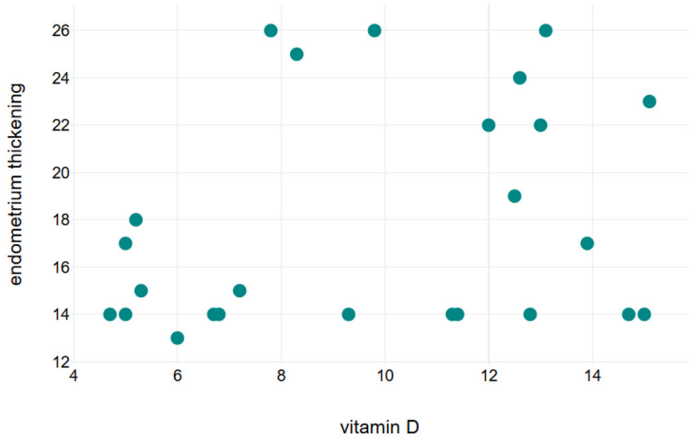

Figure 4: Dependence of endometrium thickening on vit D low levels in main group.

Discussion

We found that the majority of patients complaining of postmenopausal bleeding were over 57 years old. Additionally, the FSH levels in half of the patients with endometrial thickening were higher than the typical FSH levels expected during menopause, specifically above the range of 25.8-134.8 mIU/mL [14]. LH was elevated above 25.8 IU/L in approximately one third, while estradiol decreased below the cut-off of 16.2 ± 1.7 pg/ml in approximately half of the patients in group I and one third of the patients in group II. The average endometrial thickness in all three groups of patients was (19.23 ± 8.6), while the average vitamin D level in the groups was 14.75 ± 3.6 ng/ml, which is approximately half of lower limit of norm. This indicates the relationship between FSH, LH, estradiol and vitamin D levels.

according to our results of histopathology, 28% of cases had endometrial cancer with bleeding, endometrial hyperplasia with bleeding but without atypia was approximately in half of the patients, and only a fifth with endometrial hyperplasia cases did not have bleeding (20%).

The results of our analysis clearly demonstrate a significant relationship between vitamin D and an increase in endometrial thickness. Notably, evidence suggests that incorporating vitamin D into the treatment regimen for patients with endometrial hyperplasia can substantially improve their condition and, in some cases, even stop bleeding. This indicates a pathogenic role of vitamin D deficiency in the progression of the disease. We have previously reported that endometrial hyperplasia is often associated with obesity and insulin resistance [12,15], which suggests a hormonally and metabolically mediated influence of vitamin D on the endometrium. To data, administering 50,000 IU of vitamin D3 biweekly for 12 weeks to patients with endometrial hyperplasia resulted in significant improvements [16]. After 12 weeks, fasting plasma glucose levels decreased significantly (-1.6 ± 7.0 vs. +2.1 ± 6.1 mg/dL, P = 0.03). Additionally, insulin resistance showed improvement (-0.2 ± 0.6 vs. +0.3 ± 0.8, P = 0.01). Female patients experienced a notable reduction in serum high-sensitivity C-reactive protein (hs-CRP) levels (-1.9 ± 2.8 vs. -0.003 ± 2.0 µg/ml, P = 0.003), while total plasma antioxidant capacity significantly increased (+62.5 ± 53.5 vs. +7.5 ± 34.1 mmol/l, P < 0.001).

It is known that vitamin D maintains Ca/P ratio in blood serum, and its decrease results in various types of bleeding. Besides, vitamin D suppresses the proliferation of vascular smooth muscles, has an antifibrotic effect, modulates the immune system mediated by macrophages and cytokines [17]. Figure 3, illustrating the Pearson correlation between vitamin D and endometrial thickness, highlights an inverse relationship between serum vitamin D levels and endometrial thickness in the subjects. Furthermore, evidence to date indicates that patients with normal or suboptimal vitamin D levels exhibit a reduced severity of endometrial hyperplasia, endometrial bleeding, and cancer [3]. A study investigating the role of vitamin D in regulating cell growth in cancer suggested that vitamin D acts as an antiproliferative agent in cancer cell lines, primarily through mechanisms involving growth arrest or apoptosis. Treatment with calcitriol was found to induce cell cycle arrest in cancer cells by downregulating key regulators of cell cycle progression, such as cyclin D1 and D3, while upregulating p27, a well-established cell cycle inhibitor [18-20].

Findings

1. The level of vitamin D decreases below threshold values in cases of endometrial thickening with bleeding, both with and without neoplasia.
2. The degree of endometrial thickening is inversely proportional to the reduction in vitamin D concentration in the blood in patients with diagnosed neoplastic degeneration of the endometrium.
3. Based on our data, vitamin D supplementation is recommended for patients with endometrial thickening to prevent neoplastic degeneration of the tissue.

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