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The relation between vitamin D level, body mass index, and post-menopausal endometrial thickness

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Abstract
Background: Endometrial thickening is a commonly measured parameter on routine gynecological ultrasound and magnetic resonance image. Recent studies show there is a relation between vitamin D (vit D), obesity and the degree of endometrial thickness.
Aim of the study: To assess the relation between Vit (D) level and body mass index with post-menopausal endometrium thickness.
Patients and Method: A cross sectional study that carried out in Department of Obstetrics and Gynecology at Baghdad Teaching Hospital from the first of Jan 2020 to the end of Dec 2020. A sample of 100 post-menopausal women participated in the study after fulfilling inclusion criteria (Menopause for 12 months, endometrial thickness ≥5 mm) for each patient we did for her pelvic ultrasound for endometrial thickness, measure Vit (D) level and body mass index. The patients were divided into: - patients who had post-menopausal bleeding we did endometrial biopsy and sent for histopathology depending on the result subdivided into group I with malignant changes and group II without malignant changes and group III = patients without Vaginal bleeding.
Results: Endometrial thickness in group I was (16.15 ± 8.4) for group II was (14.3 ± 7) and for group III with significant difference found (P = 0.02), BMI were represented in group I (37.25 ± 5.15), (30.6 ± 8) for group II and (31.63 ± 7.47) in group III with no significant difference (P = 0.3), on logistic regression between these parameters and (ET) the result was significant with (vit D) with (p value = 0.02).
Conclusion: Vitamin (D) level inversely related for post-menopausal endometrial thickness, post-menopausal bleeding and probability of endometrial cancer.

Keywords: Vit D3, endometrial thickness, body mass index, post-menopausal

Introduction

Post menopause: Women are considered to be post-menopausal when they have not had their period for an entire year. It is divided into early and late menopause. Late menopause, after 70 years, is called senile [1]. Menopause, from the Greek menos (month) and pausis (cessation), is defined as the last menstrual period after a minimum of one year's amenorrhea. The average age of the female menopause (51 years) has remained unchanged since ancient Greek and Roman times even through the average lifespan has increased. Thus, an increasing number of women are now spending almost half their lifespan in a hypo-estrogenic state [2]. The endometrium is a very unique tissue because of its exquisite sensitivity to hormonal influences which it can translate morphologic changes. The histologic appearance of the endometrium varies with the age and reproduction period of women's life. When the last cycle ends in deficient proliferation or secretion, simple atrophy will appear as sparse, narrow glands lined by atrophic epithelium within a dense, fibrous stroma. Cystic atrophy becomes apparent if irregular proliferation or cystic glandular hyperplasia occurs prior to the decline in estrogen levels. In cases of protracted hormonal decline, incomplete to complete atrophy will result. After the menopause, endometrial thickening may be indicative of proliferation, cystic atrophy, simple hyperplasia, complex hyperplasia, atypical hyperplasia, or endometrial cancer [3].

Endometrial thickening (Clinical aspect)

Asymptomatic endometrial thickening

1. Post-menopausal asymptomatic endometrial thickening is defined as an endometrium >5 mm with no bleeding.
2. The endometrium is measured at its maximal thickness on midline sagittal image by

trans-vaginal ultrasound it is a bilayer measurement.
3. Asymptomatic endometrial thickness of 8-11 mm may consider as not abnormal in post-menopausal women [4].
4. Further investigations in asymptomatic women with increased endometrial thickening should be made on a case-by-case basis taking in mind: risk factors for endometrial cancer, and positive finding on Ultrasounds such as: increased vascularity, in homogeneity of endometrium over 11 mm [4].

Symptomatic endometrial thickening (Bleeding)

Table 1: Pathological findings in patients with post-menopausal bleeding [5]

Causes of post-menopausal bleeding
Endometrial/cervical polyps 2-12%
Endometrial hyperplasia 5-10%
Endometrial carcinoma 10%
Exogenous estrogens 15-25%
Atrophic endometritis and vaginitis 60-80%

Vitamin D

Vitamin D is a group of fat-soluble secosteroids responsible for increasing intestinal absorption of calcium, magnesium, and phosphate, and multiple other biological effects [6]. In humans, the most important compounds in this group are vitamin D3 (also known as cholecalciferol) and vitamin D2 (ergocalciferol) [7]. 4.1-Vitamin D metabolism It was demonstrated that keratinocytes are capable of metabolizing vitamin D to the active form because they possess the activity of 1-α-hydroxylase and 25- hydroxylase [8]. Other cells including macrophages and dendritic cells are also capable of synthesizing the active form of vitamin D, and this process is predominantly regulated by immune signals, but not by calcium or parathyroid hormone concentration. This is important because many of those cells are involved in the pathogenesis of different skin diseases [9].

Vitamin D and endometrial thickness

Some recent studies show the relation between vit D level and endometrial thickness, Tabassi Z *et al.*, revealed that vitamin D intake may reduce hyperplasia and cancer risk through modulating calcium metabolism, inhibiting cellular proliferation and induction of apoptosis in cancer cells through down regulation of telomerase activity. The active form of vitamin D, occurs in the endometrium and kidney [10]. Furthermore, endometrial tissue expresses the vitamin D receptor, a 1, 25-dihydroxyvitamin D-activated nuclear transcription factor that regulates the production of proteins involved in cell proliferation and differentiation. Therefore, these data support the hypothesis that vitamin D plays a role in the etiology of endometrial hyperplasia and cancer [6].

Vitamin D in post-menopausal women's health

Post-menopausal women have a significantly higher incidence and rate of breast cancer, cardiovascular disease, osteoporosis, vit D has protective properties against breast neoplasm, cardiovascular risks, bone health. Post-menopausal women are of particular interest as they have prevalence of diseases with relevance for vitamin D, such as musculoskeletal diseases as well as changes in vitamin D, or changes in body composition that are relevant for vitamin D status and physiology [11].

Body mass index

BMI is a mathematical formula expressed as weight (in kilograms) divided by the square of height (in meters). Based on the range value, BMI is divided into 3 categories: underweight (BMI ≤18.4), normal (BMI = 18.5-25), and overweight (BMI 23-24.9) and obesity (BMI ≥25.1, class I: from 30-34.9, class II from 35-39.9, class III BMI ≥40 kg/m2) [12].

This formula can only be applied to an individual with normal spinal structures; hence it is not appropriate to use in athletes or bodybuilders or pregnant or breastfeeding women. In relation of obesity and endometrial thickness: Obesity is an increasing problem in the world, it was informed that the prevalence in women older than 50 years were significantly increased (50%), in post-menopausal women adipose tissue is the dominant source of estrogen, increased adipose tissue in obese post-menopausal women leads to increase in estrogen, it is clear that progesterone levels decrease in post-menopausal status, decrease in progesterone is caused high level of unopposed estrogen which is a risk factor of endometrial hyperplasia and endometrial cancer [13].

In relation of obesity and vitamin D level: The menopausal transition is associated with changes in body composition and fat distribution; body fat accumulation can be demonstrated by increases in BMI, Excessive body weight is frequent complaint related to low circulating 25(OH) D levels in post-menopausal women [14].

Aim of the study

To assess the relation between Vitamin D level and body mass index and post-menopausal endometrial thickness among women attending Gyneconcology Clinic in Medical City in Baghdad Teaching Hospital.

Patients and Method

Study design and setting: A cross sectional study that carried out in Department of Obstetrics and Gynecology at Baghdad Teaching Hospital in Gynecology Clinic from the first of Jan 2020 to the end of Dec 2020. A sample of 100 symptomatic post-menopausal women participated in the study after fulfilling inclusion criteria.

Inclusion criteria: 1-Menopause for 12 months. 2-Endometrial thickness ≥5mm.

Exclusion criteria: 1-Menopausal women less than 12 months. 2-Endometrial thickening <5 mm.

Method: A hundred women were attended in Gynaecology Clinic for different reasons such as (vaginal bleeding, discharge, abdominal pain, backache) At the first all of them were sent for trans-vaginal pelvic ultrasound (the us in our hospital is PHILIPS HD 11) for assessment of endometrial thickness (ET).

If ≥5mm then depend on the history the patients divided into: - Patients who have "post-menopausal bleeding" we did endometrial biopsy by D & C and sent to Teaching laboratories in Medical City for histopathological examination. Then depending on histopathology this group subdivided into: -

Group I: With malignant tissue.

Group II: With non-malignant tissue.

Group III: Patients without vaginal bleeding.

Some patients had pelvic ultrasound and histopathology did outside our hospital for such patients we resent a new pelvic ultrasound in our hospital and review of the slide of endometrial biopsy request in teaching laboratories in Medical City.

For all patients in this study we measure body mass index and vitamin D level as following

1. BMI: Body height was measured to the nearest 0.1 cm with the patients in erect position without shoes. Body weight with indoor clothing, but without shoes, was measured to the nearest 0.1 kg. Then I divided the weight on the square of height in outpatient clinic in Baghdad Teaching Hospital.

2. Vit D: 1-2 cc of venous blood taken then separated of the sample by centrifuge in Teaching laboratory in medical city to measure vitamin D. Abbott Laboratories (Abbott Park, IL) is fully automated immunoassay for 25-hydroxy vitamin D on the Architect platform. The assay is a 1-step delayed chemiluminescent micro particle immunoassay (CMIA) with an automated online pretreatment step designed to allow vitamin D assays into routine laboratory testing workflow.

Statistical analysis

After the data were entered in a table developed by the researchers, the analysis was done by using the SPSS program, version 23 and for qualitative variables, we used frequencies and percentages, and for the quantitative variables, we used measures of central tendency and dispersion (standard deviation). For the inferential statistics, the tests were used of chi-square test (with a significance of P≤0.05).

Results

As shown in table 2, 100 patients were enrolled in the current study in which 37 (37.0%) patients were in each of age groups (<60 and 60-69) years, 21 (21%) in age group (70-79) years and only 5 (5%) patients in age (≥80) years, with mean ± SD age of the studied group was (63.4 ± 8.7) years. 58 (58%) patients were presented with bleeding and 42 (42%) with no bleeding (table 2).

Table 2: Demographic data of the studied group

Variable		No.	%
Age group	<60	37	37.0
	60-69	37	37.0
	70-79	21	21.0
	≥80	5	5.0
Age (Mean ± SD)/years		63.4 ± 8.7	
Symptom (post-menopausal bleeding)	No bleeding (Other symptoms V. discharge...)	42	42.0
	With bleeding	58	58.0

The mean of Endometrial thickness in the studied group was (14.3 ± 7.1) mm, Vitamin D was (12.6 ± 4.8), BMI was (32.6 ± 5.6), Age was (63.4 ± 8.7). All these were shown in (table 3).

Table 3: Baseline mean ± SD of different variables in the studied group

	Mean	SD
ET (mm)	14.3	7.1
vit. D	12.6	4.8
BMI	32.6	5.6
Age	63.4	8.7

Table 4, show that from 38 patients with Endometrial cancer /Endometrial hyperplasia with atypia, and 20 patients with Endometrial Hyperplasia without atypia these group present with bleeding.

Table 4: Histopathological distribution of the group I & II

Histopathology	No.	%
Endometrial cancer or endometrial hyperplasia with atypia	38	40.0
Endometrial hyperplasia without atypia	20	30.0
Total	100	100.0

Table 5 show the patients were divided into 3 groups; Group I = patients with bleeding (N = 38) with malignant change, Group II patients with bleeding without malignant change (N = 20) and Group III = patients without bleeding. The mean age of patients in Group I was (64.5 ± 9.0), and those in group II (62.5 ± 7.9) and in group III was (61.3 ± 8.2) years no significant difference was found (p = 0.07). Endometrial thickness in group I (16.15 ± 8.4) and (14.3 ± 7) for group II and group III was (11.1 ± 5) with highly significant difference between the groups (*P*<0.001).
For vitamin D it was (10.95 ± 2.9) in group I, and (11.5 ± 1.7) for group II and (12.7 ± 4.86) in group III, with significant difference found (P = 0.02). BMI were represented (37.25 ± 5.15) in group I with and (30.6 ± 8) for group II and (31.63 ± 7.47) for group III with no significant difference (P = 0.3).

Table 5: Association between different parameters according to Symptoms

	Group I (N = 38)	Group II (N = 20)	Group III (N = 42)	P value
	Mean ± SD	Mean ± SD	Mean ± SD	
Age (year)	64.5 ± 9.0	62.5 ± 7.9	61.3 ± 8.2	0.07
ET (mm)	16.15 ± 8.4	14.3 ± 7	11.1 ± 5	<0.001
vit. D	10.95 ± 2.9	11.5 ± 1.7	12.7 ± 4.86	0.02
BMI	30.25 ± 5.15	30.6 ± 8	31.63 ± 7.47	0.3

Logistic regression to assess the relation between endometrial thickness and different parameters show that; no significant association between ET and both of age and BMI with no relation, while there was a significant association with moderate relation (0.6) were found with vit D. (table 6).

Table 6: Logistic regression between many parameters with ET

Parameters	ET (r)	ET (P-value)
Age	0.106	0.4 Ns
BMI	0.196	0.6 Ns
Vit D	0.6	0.02 S

Discussion

Endometrial thickening is a commonly measured parameter on routine gynecological ultrasound and magnetic resonance image. The appearance, as well as the thickness of endometrium, will depend on whether the patient is of reproductive age or in post menopause [15]. Our study shows: -

1. That most of the patients who attending Gynaecology Clinic complaining from post-menopausal bleeding (PMB) and the age of the majority was more than 60 years as shown in Table (2).
2. The mean of Endometrial thickness in the studied group was (14.3 ± 7.1) which is high and vitamin D was (12.6 ± 4.8) which less than normal levels This may be due to (lack of vitamin D and calcium in the diet often in conjunction with inadequate sun exposure, have a disease in the intestine making it inability to absorb vitamin D, inability to process vitamin D to active form due to kidney or liver disease …) and The mean of BMI was (32.6 ± 5.6) as show in table (3), so most of our patients in this study were overweight or obese this may be due to (change in her life style, have multiple disease and bedridden, have osteoporosis with limitation of movement, loss of her partner and depression..).
3. Most of the women that complaining from (PMB) the results of the histopathology were 38% endometrial cancer endometrial hyperplasia with atypia and 20% endometrial hyperplasia without atypia as show in table (4), this high Discussion 31 percentage of malignancy may be because most of the patients were referral from other hospitals to our tertiary center.
4. Apparently the result in table (5) there is no significant association between all studies groups and the age and BMI, as for BMI, which is not in agreement with research in 2016 about BMI and endometrial cancer by measuring of BMI that if it was >3035 kg /m2 associated with a 4-7-fold increase compared to normal weight women [16].
5. On the other side the result in table (5) there is significant association between vitamin D and Endometrial thickness. This agreement to Maryam Chamani's research in March 2017 about VD supplement in Endometrial hyperplasia, demonstrated patient with HP taking one dose of 50,000 iv VD every 2 weeks for 12 weeks compare with placebo result in improvement of biomarker information and oxidative stress and fasting blood glucose and C-reactive protein [17].
6. When applying the logistic regression in table (6), there is a significant inverse relation between vitamin D (vit D) and Endometrial thickness (ET), patients who had vitamin D deficiency they had increase in Endometrial thickness, and may present with vaginal bleeding the majorities of the patients with endometrial cancer will presented with lower Vitamin D level, One the other hand, the patients with normal or subnormal level of vitamin D had decrease in ET, the vaginal bleeding, and the endometrial cancer. Discussion 32 so may be the giving of vitamin D supplement to the patients in this age group will lower these different symptoms. Similar studies, in 2014 the role of vitamin D in control of cell growth in endometrial cancer proposed that vitamin D as antiproliferative drug in endometrial cancer cell lines, mainly reporting a mechanism of growth arrest or apoptosis. Calcitriol treatment induced cell cycle arrest in endometrial cancer cells suppressing some regulators of cell cycle progression such as cyclin D1 and D3 and increasing the expression of p27, a well-known cell cycle inhibitor [18].

By Multidisciplinary Digital Publishing Institute (MDPI) and the international journal of molecular sciences, in august 2018 the study was about vitamin D and Endometrium show (VD was demonstrated to be able to induce a programmed cell death in endometrial cancer cells activating key actors of intrinsic apoptotic pathway such as caspase 3 and 9 proteases and by disrupting the delicate balance Between pro apoptotic factor and pro survival defense response [6]. Yabushita and colleagues demonstrated that VD as cell differentiation inducing agent in endometrial cancer cells, after exposure to active form of VD for 6 days expressed high levels of cytokeratin polypeptide and become columnar with pronounced polarity and formed gland like structures when cultured in collagen gel [19].

In agreement with Asadi M, *et al.* in his study to detect the effect of vitamin D to improve the endometrial thickness in patients with poly cystic ovarian disease found that there is statistical difference in endometrial thickness between those patients treated with vitamin D and those who had received placebo [20].

Conclusion

Vitamin D level inversely related to post-menopausal endometrial thickness, post-menopausal bleeding and probability of endometrial cancer.

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