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The Connection of the Level of Estradiol in Serum and Obesity with the Endometrial Bleeding in Postmenopausal Women

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Abstract

BACKGROUND: Postmenopausis is a period that begins one year after the last menstrual period. Abnormal uterine bleeding could be of different origins.

AIM: This study aimed to determine the association of serum estrogen hormone levels and obesity with the occurrence of endometrial bleeding in post-menopausal women.

MATERIAL AND METHODS: Prospective clinical study involving 120 postmenopausal patients treated at the University Clinic for Gynecology and Obstetrics-Skopje, divided into two groups: control and study. The control group consisted of 40 postmenopausal patients without endometrial bleeding, hospitalised and operated due to urogenital pathology. The study group consisted of 80 patients with endometrial bleeding who were divided into three subgroups according to the thickness of the endometrium: from 5-8 mm, 8-11 mm and above 11 mm. In all subjects, estradiol and BMI was determined.

RESULTS: Estradiol levels were statistically higher in the study group compared to control while statistically significant difference among the three subgroups according to the thickness of the endometrium about the levels of estradiol in blood is not found. About BMI, the results showed that there was no statistical significance between the two examined groups.

CONCLUSION: Patients with endometrial bleeding have increased levels of estradiol and are at increased risk of endometrial cancer about controls, the likelihood of endometrial cancer significantly increases by 1,108 times.

Introduction

Over the last 30 years, there has been an increased incidence of endometrial malignancy in the world, and especially in highly developed countries. The incidence of postmenopausal women is the highest with a peak of 85% in the age group 55-63 [1], [2]. Postmenopausis is a period that starts one year after the last menstrual period. It is divided into early and late menopause. Late menopause, after 70 years, is called senile. Almost 5% of all the visits by a gynaecologist are due to postmenopausal bleeding [3]. During this period, abnormal uterine bleeding may range from polyps, endometrial atrophy, endometrial hyperplasia, endometrial cancer, submucosal fibroid, hormone therapy, uterine infections or cervix, use of certain medications such as blood thinners [4], etc. In most cases, endometrial bleeding is associated with endometrial polyps (6% of cases) [5] or endometrial atrophy (almost 50% of cases) [6]. Studies suggest that only 3.7%-17.9% of cases with postmenopausal bleeding are due to endometrial cancer [7].

Ultrasonography is widely used as a diagnostic method for evaluating irregular bleeding in postmenopausal women [8]. For the time being, there is no consensus on the limit value of endometrium thickness in which there is no need for sampling for analysis in cases of endometrial bleeding [8]. In postmenopausal ovaries, they have no more follicles, thus stopping the production of estradiol and progesterone. The value of oestradiol in postmenopausis ranges from 10 to 20 pg/mL. According to the results of many studies, oestradiol is

a significant predictor of endometrial malignancy and endometrial bleeding [8], [9]. According to Naomi's study and chronic endometrial malignancy, endometrial bleeding in patients in menopause is positively associated with an elevated estradiol level [9].

Obesity is also strongly associated with the development of endometrial bleeding [10]. Almost 57% of endometrial bleeds in the United States are due to overweight [11], [12]. The meta-analysis involving 26 studies, the American Cancer Research Institute, found that an increase in Body Mass Index (BMI) by five units increases the risk of endometrial bleeding by 50% [13]. The mechanism of action of obesity as a risk factor for endometrial bleeding in postmenopausal women is explained by the increased adiposity that increases the activity of aromatase, which leads to the conversion of androgenic hormones into estrogens and directly promotes the proliferation of endometrium and transcription of the pro-proliferative genes. Chronic inflammation associated with visceral adiposity is mediated by proinflammatory adipokines and leads to hyperinsulinemia, to an increase in insulin-like growth factor 1 (IGF1) and hyperglycaemia, which increases endometrial proliferation. At the same time, reduction of anti-inflammatory cytokines was observed. Inflammation and an increase in estrogen metabolites additionally contribute to DNA damage and genetic instability. Finally, stem cells can be recruited from the adipose tissue, where they contribute to supporting the tumour. The purpose of this study was to determine the eventual difference in the level of serum estrogen hormones, i.e. obesity in endometrial bleeding in postmenopausal women.

This study aimed to determine the association of serum estrogen hormone levels and obesity with the occurrence of endometrial bleeding in post-menopausal women.

Material and Methods

This is a prospective clinical study involving 120 postmenopausal patients treated at the University Clinic for Gynecology and Obstetrics-Skopje. Patients were divided into two groups: control and examination group. The control group included 40 postmenopausal patients without endometrial bleeding, hospitalised and operated due to urogenital pathology, and with an orderly histopathological finding of the material obtained with an explorative endometrial curettage. The study group included 80 postmenopausal patients with endometrial bleeding. According to the ultrasound verified thickness of the endometrium, they were divided into three subgroups: from 5 -8 mm, 8-11 mm and above 11 mm. Each patient was given a detailed history, weight and height were determined for BMI calculation and 5 mL of venous blood was taken to determine the serum estradiol level. This study excluded patients who received hormone replacement therapy, patients to whom fractional explorative curettage cannot be performed, patients with a personal history of malignant diseases, benign or malignant ovarian changes and patients who were operated of breast cancer under treatment with tamoxifen.

The concentration of oestradiol in serum was determined by the chemiluminescent method of the Immulite 2000 analyser in the biochemical laboratory at the University Clinic for Gynecology and Obstetrics Skopje. For the reference values of oestradiol in postmenopausis, values of 4 to 71.2 pg/mL were taken. Ultrasound analysis was performed with an ultrasonic device Voluson E8, and the measurement was done with a transvaginal probe whereby the patients were in the supine position at the gynaecological chair. The examination was performed on an empty bladder with a probe for each patient separately. All the analyses were made in a longitudinal section of the uterus, where both the cervix and the fundus of the uterus are displayed simultaneously, and the endometrial media line is also visualized.

Quite often in the study was voluntary and anonymous without any procedures or conditions that imply coercion and it was approved by the responsible bodies of the Medical Faculty at the Ss Cyril and the Methodius University of Skopje, Skopje.

Statistical analysis

All tests were performed with SPSS 20.0. Continuous variables were described using mean and standard deviation (SD) or median and interquartile range. Categorical variables were described using frequencies and percentages. Data were tested for normality by Shapiro-Wilk tests and graphically checked for symmetry. Differences between groups were assessed by Mann-Whitney U tests and Kruskal-Wallis ANOVA test. P values < 0.05 was set as the threshold for statistical significance.

Results

The average blood estradiol level among the examinees in the sample was 29.8 ± 14.1 pg/ml with a minimum value of 20 pg/mL and a maximum value of 99.5 pg/mL. In the control group, the mean estradiol level in the blood was 25.5 ± 12 pg/mL with a minimum value of 20 pg/ml and a maximum value of 80.9 pg/mL. In patients in the test group with endometrial bleeding, the mean blood estradiol concentration was 31.9 ± 14.7 pg/mL with a minimum

value of 20 pg/mL and a maximum value of 99.5 pg/mL and was significantly elevated relative to the control group, $p < 0.05$ (Mann-Whitney U Test: $Z = 3.9108$, $p = 0.00009$). In 50% of patients in the test and control group the blood estradiol value was greater than the corresponding IQR = 29 pg/mL (21.9-34.9) vs. IQR = 20 pg/mL, Table 1 (20-25 pg/mL).

Table 1: Concentration of serum estradiol (pg/mL) in the control and examination group

Group	Number n	Mean value	SD	Minimum	Maximum	Mediana IQR
Control	40	25.48	11.98	20	80.9	20 (20-25)
Examination	80	31.95	14.72*	20	99.5	29 (21.9-34.9)
Total value	120	29.79	14.15	20	99.5	26 (20-32.7)

According to the division of patients from the study group into three subgroups according to the thickness of the endometrium, an analysis of blood estradiol values was performed in each of these groups, Table 2. In the first subgroup, with a thickness of endometrium 5-8 mm, blood estradiol was 30 ± 11.5 pg/mL with a minimum value of 20 pg/mL and a maximum value of 66 pg/mL. According to the media analysis, 50% of patients in this subgroup had a blood estradiol value greater than IQR = 27.1 pg/mL (20.8-32.5 pg/mL). In the second subgroup with an endometrial thickness of 8 mm-11 mm, the mean value of oestradiol in the blood accounted for 33.3 ± 19.2 pg/mL with a minimum value of 20 pg/mL and a maximum value of 87 pg/mL. According to the analysis of the media, 50% of patients in this subgroup had a blood estradiol value greater than IQR = 28.8 pg/mL (21.5-36 pg/mL). In the third subgroup with a thickness of endometrium > 11mm, the mean blood estradiol concentration was 33.6 ± 15.7 pg/mL with a minimum value of 20 pg/mL and a maximum value of 99.5 pg/mL. According to the media analysis, 50% of patients in this subgroup had a blood estradiol level greater than IQR = 29.6 pg/mL (25.4-36.3 pg/mL). Statistical analysis of the results showed that there was no significant significance in blood concentrations of estradiol in patients with different endometrial thickness (Kruskal-Wallis ANOVA: $H = 1.815984$ $p = 0.4033$), Table 2.

Table 2: Blood oestradiol concentrations (pg/mL) in patients with different endometrial thickness

Subgroups Endometrial thickness (mm)	Number N	Mean value	SD	Minimum	Maximum	Mediana IQR
5 – 8	36	30.03	11.47	20	66	27.1 (20.8-32.5)
8 – 11	17	33.35	19.17	20	87	28.8 (21.5-36)
> 11	27	33.64	15.67	20	99.5	29.6 (25.4-36.3)
Total value	80	31.95	14.72	20	99.5	29.2 (21.9-34.9)

Within the research, the respondents in the whole sample were analysed according to the BMI value. The average BMI value in the entire sample was 29.2 ± 4.9 kg/m^2 with a minimum value of 14.9 kg/m^2 and a maximum value of 42.7 kg/m^2, Table 3. According to the IQR, 50% of patients in the whole sample had BMI with a height greater than 29.3 kg/m^2.

Table 3: Values for BMI (kg/m^2) in the control and examination group

Group	Number	Mean Value	Sd	Minimum	Maximum	Mediana IQR
Examination	80	29.46	5.42	14.9	42.7	29.7 (26-32.3)
Control	40	28.66	3.85	21.8	41.4	28.2 (26.1-30.3)
Total value	120	29.19	4.95	14.9	42.7	29.3 (26-32)

The statistical analysis of the BMI results showed that there is no statistical significance between the two groups of patients. Patients in the examined group had an average BMI of 29.5 ± 5.4 kg/m^2 with a minimum value of 14.9 kg/m^2 and a maximum of 42.7 kg/m^2. According to the median analysis (IQR), 50% of patients in this group had a BMI value greater than 29.7 kg/m^2. In the control group, the average BMI of the patients was 28.7 ± 3.8 kg/m^2 with a minimum value of 21.8 kg/m^2 and a maximum value of 41.4 kg/m^2. According to the median (IQR), fifty per cent of the subjects in the control group had a BMI value greater than 28.2 kg/m^2.

Discussion

Estradiol is a significant predictor of endometrial malignancy, especially in patients with endometrial bleeding. The results of serum estradiol levels in this study showed that according to the media analysis, 50% of patients in this subgroup had an estradiol level greater than IQR = 29.6 pg/mL (25.4-36.3 pg/mL), which can be assumed to be at increased risk of endometrial cancer. Studies of Naomi et al., suggest a positive association between endometrial malignancy in postmenopausal patients and the level of estradiol [9]. Under the influence of relatively high levels of estrogen stimulation, postmenopausal endometrium may develop mild architectural changes and turn into so-called impaired proliferative endometrium [14] or may show an increase in degrees of architectural and cytological atypia and have a form of atypical endometrial hyperplasia (endometrial intraepithelial neoplasia) [15] or endometrial intraepithelial carcinoma [16] from which endometrial cancer can develop.

The endometrial carcinoma shows a positive association with the increased body mass index, so in 39% of cases with endometrial cancer is in obese women [17]. Several mechanisms can promote endometrial cancer or progression in overweight or obese women. Primarily, this association can be explained by an increase in circulating estrogens arising from the aromatisation of androgenic precursors in adipose tissue, leading to endometrial cell proliferation [18]. The data in the consulted literature coincide with the results of this study. Thus, in the study of Widderpas et al., [19], it was found that the assembled patients with BMI of 30-33.9 kg/m^2 had

a three-fold risk of developing endometrial malignancy, which is consistent with the results in this study in which the statistical analysis showed that for each unit an increase in BMI, the probability of endometrial carcinoma increased by 1.484 times (p = 0.0001, 95% CI = 1.205-1.829).

In conclusion, concentration of serum estradiol in patients with bleeding (31.9 ± 14.7 pg/mL) was statistically significantly elevated relative to the control group, (25.5 ± 12 pg/mL), $p < 0.05$. Among the subgroups of patients with different endometrial thickness, statistical significance for the concentration of oestradiol in serum was not found. No statistical significance was found for the values of the body mass index between the control group (28.7 ± 3.8 kg/m^2) and the test group (29.5 ± 5.4 kg/m^2), but the values are in between obesity and obesity. If it is known that increased body mass, that is, obesity and increased concentrations of estrogen hormones are a risk factor for developing malignancy of the endometrium, then both groups of subjects are at increased risk of endometrial cancer.

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